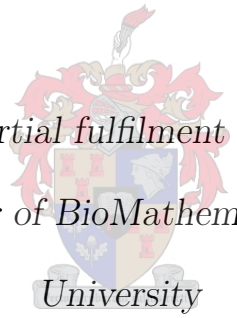
Modelling the transmission dynamics of Multi-strains Influenza with Vaccination and Antiviral Treatment

by

Dephney Mathebula



Thesis presented in partial fulfilment of the requirements for the degree of Master of BioMathematics at Stellenbosch University

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Abstract

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Thesis: MScMath (Biomathematics)

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Recently, new strains of influenza such as bird flu and swine flu have emerged. These strains have the capacity to infect people on a quite large scale and are characterized by their resistance to existing influenza treatment and their high mortality rates.

In this thesis, we consider two models for influenza transmission dynamics that include both sensitive and resistant strains and accounts for disease induced mortality.

The first model allows for immigration/migration and does not include any control measure. The second one explores the effects of vaccination and treatment of the sensitive strain but ignores immigration/migration.

We studied the two models mathematically and numerically. We started with the model without any control measures; we calculated the basic reproductive numbers, determined the equilibrium points and investigated their stability. Our analysis showed that when the basic reproduction numbers of both strains are less than one then the two strains will die out. When at least one of the basic reproduction numbers is greater than one, then the strain with the higher basic reproduction number is the one that will persist. Numerical simulations were carried out to confirm the stability results and a bifurcation diagram was given. We also studied numerically the impact of the mortality rate of influenza on the dynamics of the disease. Especially, we investigated the effect of the mortality rate on the time needed for the pandemic to reach its peak, the value at the peak for each strain and, when eradication is possible, the time it takes for the disease to be eradicated.

For the model with control, we also calculated the control reproductive number and the equilibrium points. The stability analysis was carried out numerically and bifurcation diagrams with vaccination and treatment parameters were given to determine the regions where eradication of the disease is possible.

Our results suggest that in the presence of a resistant strain, treating more infected individuals will not eradicate the disease as the resistant strain will always persist. In such a case vaccination and antiviral treatment should be implemented simultaneously.

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Dedications

I dedicate this work to my parents.

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Chapter 1

Introduction

1.1 Overview of influenza dynamics

Influenza is a respiratory infection in mammals and birds. It is caused by an RNA virus in the family Orthomyxoviridae family [14, 10]. Human influenza viruses can be passed to other people by exposure to infected droplets expelled by coughing or sneezing that can be inhaled, or that can contaminate hands or surfaces. Individuals incubate the virus for roughly one to three days before becoming infectious after initial infection [24]. Infectiousness can precede clinical disease by approximately one day. The infectious period is typically three to six days, whereas the duration of the disease is typically two to seven days. Most individuals recover from influenza and are believed to retain lifelong immunity to strains closely related to the infecting strain. The virus is divided into three main types (A, B and C), which are distinguished by differences in two major internal proteins [24]. Influenza virus type A is the most significant and interesting from an epidemiological, ecological and evolutionary

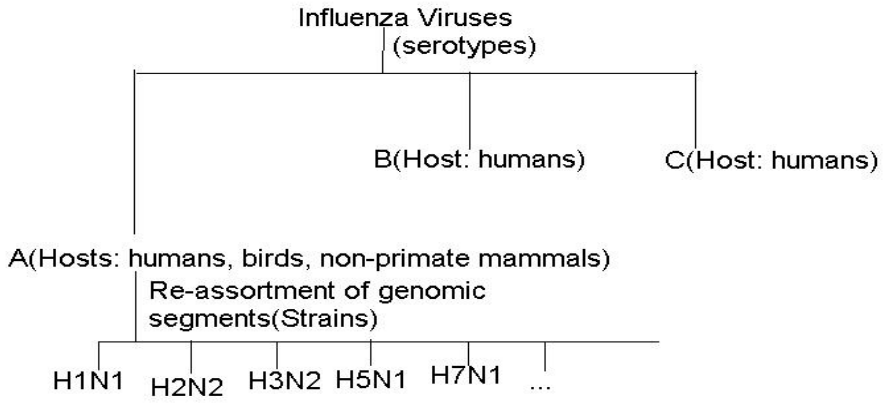


Figure 1.1: Types and known strains of human influenza viruses [23].

standpoint because it is found in a wide variety of bird and mammal species and can undergo major shifts in immunological properties. Type B is largely confined to humans and is an important cause of morbidity. Little is known about type C, which is not an important source of morbidity. Surprisingly little is known about the transmission of influenza, and the importance of airborne transmission relative to droplet transmission remains controversial [24].

Currently there are two subtypes of type A influenza virus circulating in humans, namely, H1N1 and H3N2 [23]. The H1N1 subtype of influenza which is commonly known as swine flu is caused by H1N1 influenza A virus, is a combination of swine, avian and human influenza viruses. The symptoms of H1N1 are usually mild, but they can become severe, leading to pneumonia or respiratory failure. The H3N1 subtype of influenza is also a strain of the type A influenza virus that can cause illness in humans. The severity of symptoms can vary but usually involves respiratory and constitutional (e.g. headache,

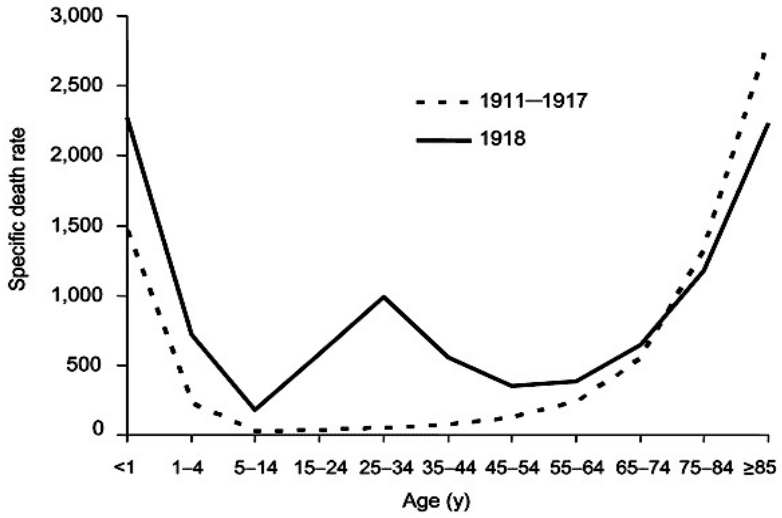


Figure 1.2: "U-" and "W-" shaped combined influenza and pneumonia mortality, by age at death, per 100 persons in each age group, United States, 1911-1918. Influenza- and pneumonia specific death rates are plotted for the inter-pandemic years 1911-1917(dashed line) and for the pandemic year 1918(solid line) [1].

aching muscles) symptoms [17]. Influenza has been a major cause of morbidity and mortality. Three influenza pandemics that lead to the death of 40-50 million people. Fortunately, subsequent pandemics of the twentieth century were not as severe as the Spanish Flu. For instance, the Asian Flu of 1957 killed about 2 million people while the Hong Kong Flu (1968) killed around 1 million people [1].

Influenza epidemics can seriously affect all age groups annually, but the highest risk of complications occur among children younger than age two, adults aged 65 or older, pregnant women and people of any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood or metabolic diseases such as diabetes, or weakened immune system [24, 17]. The curve of influenza deaths by age at death has historically, for at least 150 years, been U-shaped

as in figure (1.2), exhibiting mortality peaks in the very young and the very old, with a comparatively low frequency of death at all ages in between.

As of June 2010, worldwide more than 214 countries and communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18, 209 deaths [3].

National authorities confirmed deaths of 14,286 in 2009 worldwide. World Health Organization (WHO) states that mortality caused by the new H1N1 strain is unreported. The Centre for Disease Control (CDC) estimated 9,820 death caused by swine flu by November 2009 in the United States of America [12].

Influenza can cause serious public health and economic problems [24, 17]. In developed countries, epidemics can result in high levels of worker absenteeism and productivity losses. In communities, clinics and hospitals can be overwhelmed when large numbers of sick people appear for treatment during peak illness periods. While most people recover from influenza, there are large numbers of people who need hospital treatment and many who die from the disease every year. Unfortunately, little is known about the effects of influenza epidemics in developing countries such as South Africa.

1.2 Vaccination and antiviral treatment for influenza

Human influenza vaccination was first introduced in the 1940's, representing a breakthrough in the struggle against influenza. In 1942, clinical trials car-

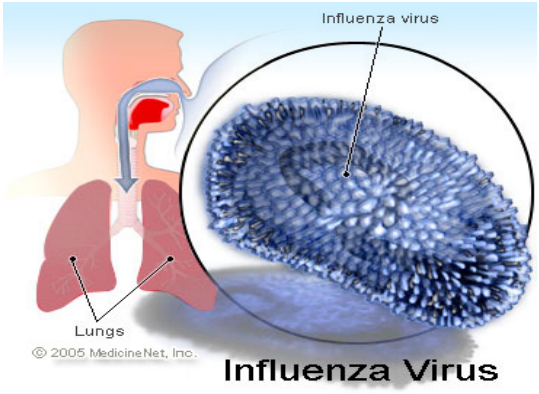


Figure 1.3: Influenza virus [23].

ried out by the US Army confirmed the usefulness of vaccination in reducing morbidity and mortality due to influenza [7]. The failure of current influenza vaccines to protect all vaccine recipients warrants the determination of conditions necessary for a substantial reduction and possible eradication of influenza infection [4].

Influenza vaccination is the most effective method for preventing influenza virus infection and its potentially severe complications [4]. Influenza immunization efforts are focused primarily on providing vaccination to persons at risk for influenza complications and to contacts of these persons. Influenza vaccine may be administered to any person aged less than 6 months to reduce the likelihood of becoming ill with influenza or of transmitting influenza to others; if vaccine supply is limited, priority for vaccination is typically assigned to persons in specific groups and of specific ages who are, or are contacts of, persons at higher risk for influenza complications. Trivalent Inactivated Influenza

Vaccine (TIV) may be used for any person aged less than 6 months, including those with high-risk conditions. Live, Attenuated Influenza Vaccine (LAIV) is currently approved only for use among healthy, nonpregnant persons aged 5-49 years. Because influenza viruses undergo frequent antigenic change, persons recommended for vaccination must receive an annual vaccination against the influenza viruses currently in circulation.

Although vaccination has been an effective strategy against influenza infection, current preventive vaccines consisting of inactivated virions do not protect all vaccine recipients equally [4]. Vaccine-based protection is dependent on the immune status of the recipient. Typically, influenza vaccines protect $70\%-90\%$ of healthy young adults and as low as $30\% - 40\%$ of the elderly and others with weakened immune systems such as HIV-infected or immuno-suppressed transplant patients. Furthermore, due to the seasonal drift in the viral genome, annual vaccination against the influenza virus strains anticipated to be in circulation during the upcoming season is necessary to prevent new infections and subsequent outbreaks.

Although vaccination coverage has increased in recent years for many groups recommended for routine vaccination, coverage remains unacceptably low. Strategies to improve vaccination coverage, including use of reminder or recall systems and standing order programs should be implemented or expanded [11]. Human influenza treatment includes a range of medications and therapies that are used in response to influenza [16]. Treatments may either directly target the influenza virus itself, or simply offer relief to symptoms of the disease, while the body's own immune system works to recover from infection. The two main classes of antiviral drugs used against influenza are neuraminidase

inhibitors, such as zanamivir and oseltamivir, or inhibitors of the viral M2 protein, such as amantadine and rimantadine. These drugs can reduce the severity of symptoms if taken soon after infection and can also be taken to decrease the risk of infection. The failure of current influenza vaccines to protect all vaccine recipients warrants the determination of conditions necessary for a substantial reduction and possible eradication of influenza infection [4].

Antiviral medications are complementary to vaccination and are effective when administered as treatment and chemoprophylaxis after an exposure to influenza virus [11].

1.3 Motivation of the study

Because there is the high risk for the influenza pandemic and large number of deaths associated with influenza, it is imperative to increase our understanding of the influenza disease dynamics. Mathematical models have provided a useful tool to gain insights into the transmission and control of the disease [18]. These insights can potentially help us assess the effectiveness and implications of various preventive and control strategies. They also allow us to investigate hypotheses about the mechanisms responsible for epidemics and to reject hypotheses that yield predictions that are inconsistent with documented epidemic patterns.

Historically, models with different strains of influenza virus have been studied, but most of them have considered sensitive and resistant strains without taking into consideration that infected individuals can die due to influenza, for

instance, swine flu has shown a very high mortality for the past years. In this study we consider a model that includes a strain that induces a relatively high mortality and may be drug resistant. The model will be used to determine minimum proportion of individuals to be treated and vaccinated in order to eradicate the disease.

1.4 Overall aim of the study

To gain more insights about the impact of antiviral treatment and vaccination in eradicating the spread of influenza virus among human population.

1.5 Objectives of the study

- To determine the potential impact of antiviral treatment and vaccination for sensitive and resistant strains of the influenza virus.
- To determine if the use of antiviral treatment reduces the size or delays the peak of the pandemic.
- To compare the influenza transmission dynamics when control measures are implemented and when they are not implemented.
- To inform and assist policy-makers in designing proper interventions and targeting treatment resources for maximum effectiveness.

1.6 Methodology

We study two compartmental models that describe the transmission dynamics of influenza virus among the human population. The first model represents the transmission dynamics of influenza virus when the control measures are not implemented. The last model is the extension of the first one whereby we incorporate disease induces mortality and resistant strain. The models will be studied both analytical and numerically.

Thesis outline

- Chapter 1 provides overview of influenza virus, vaccination and intiviral treatment for influenza.
- Chapter 2 provides review of several recent studies on influenza that studied different influenza prevention and control measures including vaccination, antiviral treatment, quarantine, isolations and media coverage.
- Chapter 3 provides an SIR model that describes influenza transmission dynamics where control measures are not implemented and it is the modification of the model in [13] by Zhen Jin and his colleagues.
- Chapter 4 provides the main model of our study which represents influenza transmission dynamics where control measures are implemented.

Chapter 2

Literature Review

2.1 Influenza models

Mathematical models have been extremely useful in understanding the transmission dynamics of influenza. They have been providing assistance in evaluating the potential effectiveness of public health interventions in controlling pandemics of varying severity. Severity is defined by the value of R_0 (the basic reproduction number). They have also been used for the development and implementation of infection control policies to combat outbreaks and epidemics of communicable viral diseases such as influenza.

Several recent studies on influenza modelling have focused on the influence of prevention and control measures including vaccination, antiviral use, quarantine, and isolations [18, 15]. These models have provided useful information about the impact of various control measures in the disease dynamics. However, most of these models have considered either vaccination or antiviral use

alone, and vaccination and antiviral treatment. Kermack and McKendrick developed the first Susceptible-Infectious-Recovered (SIR) mathematical model that could be used to describe an influenza epidemic [8]. The is SIR model has been used as a basis for all influenza models. The simplest extension to the SIR model includes demographics, specifically inflow and outflow of individuals into the population. Analysis of this demographic model shows that influenza epidemics can be expected to cycle, with damped oscillations, and reach a stable endemic level. In [9, 20] the SIR model was modified to include seasonality. This gave rise to a model that captured the sustained cycles of influenza epidemics. The SIR model has also been extended in order to predict the spatial dynamics of an influenza epidemic. The first spatialtemporal model of influenza was developed in the late 1960s by Rvachev [19]. He connected a series of SIR models in order to construct a network model of linked epidemics. He then modelled the geographic spread of influenza in the former Soviet Union by using travel data to estimate the degree of linkage between epidemics in major cities.

In the 1980s, Rvachev and his colleagues Baroyan and Longini extended his network model by including biomedical interventions such as vaccination, prophylactic treatment with antivirals, and therapeutic treatment [8]. It has been shown that once interventions are included in the model, a Reproduction Control Number (R_C) can be determined. R_C is defined as the average number of new infections that one infectious case generates, in an entirely susceptible population when an intervention is in place, during the time they are infectious. The value of R_C will depends on both the strength of the intervention and the severity of the epidemic in the absence of the intervention (R_0). The

quantity R_C will always be less than R_0, but if $R_C < 1$, the intervention will cause the epidemic to die out, whereas if $R_C > 1$ the intervention will only reduce the severity of the epidemic.

In [21], a deterministic transmission and vaccination model was studied to investigate the effects of media coverage on the transmission dynamics of influenza. The model included the effect of media coverage on reporting the number of infections as well as the number of individuals successfully vaccinated. The have used the basic reproduction number to discuss the local stability of the disease-free equilibrium. They have also investigated the impact of costs that can be incurred, which include vaccination, education, implementation and campaigns on media coverage using optimal control theory. Their model shown that the media trigger a vaccinating panic if the vaccine is imperfect and simplified messages result in the vaccinated mixing with the infectives without regard to disease rick. Therefore the effects of media on an outbreak are complex. Simplified understanding of disease epidemiology, propagated through media sound-bites, may make the disease significantly worse.

In [5], a stochastic model of pandemic influenza was used to investigate realistic strategies that can be used in reaction to developing outbreaks. The model was calibrated to documented illness attack rates and basic reproductive number ($R0$) estimates, and constructed to represent a typical mid-sized North American city. The model predicted an average illness attack rate of 34.1% in the absence of intervention, with total costs associated with morbidity and mortality of US dollars 81 million for such a city. Attack rates and economic costs can be reduced to 5.4% and US dollars 37 million, respectively, when low-coverage reactive vaccination and limited antiviral use are

combined with practical, minimally disruptive social distancing strategies, including short-term, as-needed closure of individual schools, even when vaccine supply-chain-related delays occur. Results improve with increasing vaccination coverage and higher vaccine efficacy.

In [4] a deterministic compartmental mathematical model was constructed to study the transmission dynamics of influenza. The model was analysed qualitatively to determine criteria for control of an influenza epidemic and was used to compute the threshold vaccination rate necessary for community-wide control of influenza. Using two specific populations of similar sizes, an office and a personal care home, the model showed that the spread of influenza can be controlled if the combined effect of the vaccine efficacy and vaccination rate reaches a threshold determined by the duration of infectiousness and the rate of contact between infected and susceptible individuals .

In [15] a deterministic compartmental model of the transmission of oseltamivir sensitive and resistant influenza infections during a pandemic was designed and analysed. The model described a homogeneous population of pandemic influenza and the control measures prophylaxis and treatment. Vital dynamics such as births and deaths were not taken into consideration. The model predicted that even if antiviral treatment or prophylaxis lead to the emergence of a transmissible resistant strain in as few as 1 in 50,000 treated persons and 1 in 500,000 prophylaxed persons, widespread use of antivirals may strongly promote the spread of resistant strains at the population level [15]. On the other hand, even in circumstances in which a resistant strain spreads widely, the use of antivirals may significantly delay and reduce the total size of the pandemic. If resistant strains carry some fitness cost, then, despite widespread emergence

of resistance, antivirals could slow pandemic spread by months or more, and buy time for vaccine development. This delay would be prolonged by non-drug control measures such as social distancing that reduce transmission, or use of a stockpiled suboptimal vaccine. Surprisingly, the model suggested that such non-drug control measures would increase the proportion of the epidemic caused by resistant strains. Their model suggested that benefit of antiviral drug use to control an influenza pandemic may be reduced, although not completely offset, by drug resistant in the virus. Therefore the risk of resistance should be considered in pandemic planning and monitored closely during a pandemic.

Zhipeng and Zhilan [18] adapted a similar structure as that in [15]. They introduced a vaccinated class, included vital dynamics, neglected prophylaxis and considered only drug treatment. The main purpose of their model was to explore the interaction between vaccination and drug use. They found that higher levels of treatment may lead to an increase of epidemic size, and the extend to which this occurs depends on other factors such as the rates of vaccination and resistance development. This simply implies that treatment should be implemented appropriately.

Summary

In this chapter we reviewed several recent studies on the influence of different influenza prevention and control measures including vaccination, antiviral treatment, quarantine, isolations and media coverage. However, in this study we will only consider the use of antiviral treatment and vaccination as the con-

trol measures in order to gain more insights on the implementation of control measures.

Chapter 3

Influenza model without control measures

In this chapter we consider a compartmental model that describes the transmission dynamics of influenza, where control measures such as quarantine, vaccination and treatment are not implemented. We consider the resistant and sensitive strains, and recruitment into each class. This model is a slight modification of the model in [13], whereby only the transmission dynamics of influenza between susceptible, exposed, infected and recovered individuals were considered. This model accounts for resistant strains and emergency strain that may cause death.

Since in this chapter we are not considering any treatment, we should refer to the two strains as sensitive and resistant strains, we could have called them just strain 1 and 2, but since we will introduce treatment in Chapter 4 and for notations convenience we refer them as sensitive (s) and resistant (r) strains.

3.1 Model formulation

The compartmental model (3.1) describes the flow of four different population classes. Let N denote the total population size. We divided N into four disjoint classes: susceptible individuals (S), individuals infected with the sensitive strain (I_s), individuals infected with the resistant strain (I_r) and recovered individuals (R). Then the total population is given by

$$N = S + I_s + I_r + R.$$

Individuals are recruited into the susceptible class at a rate Λ either through birth or immigration. Susceptible individuals either die due to natural causes at a rate μ or progress to the class of individuals infected with the resistant and sensitive strains at the rates λ_s and λ_r respectively. Infected individuals in the $I_j(j = r, s)$ class recover at a rate k_j. The model also consider immigration by considering a constant rate of individuals moving into (or out of) the infected individuals classes and recover class.

The model equations are as follows

$$\begin{cases} \frac{dS}{dt} = \Lambda - \mu S - \lambda_s S - \lambda_r S, \\ \frac{dI_s}{dt} = \Lambda_s + \lambda_s S - (\mu + d_s + k_s) I_s, \\ \frac{dI_r}{dt} = \Lambda_r + \lambda_r S - (\mu + d_r + k_r) I_r, \\ \frac{dR}{dt} = \Lambda_R + k_s I_s + k_r I_r - \mu R \end{cases} \tag{3.1.1}$$

where $\lambda_s = \frac{\beta_s I_s}{N}$ and $\lambda_r = \frac{\beta_r I_r}{N}$ with $N = S + I_s + I_r + R$.

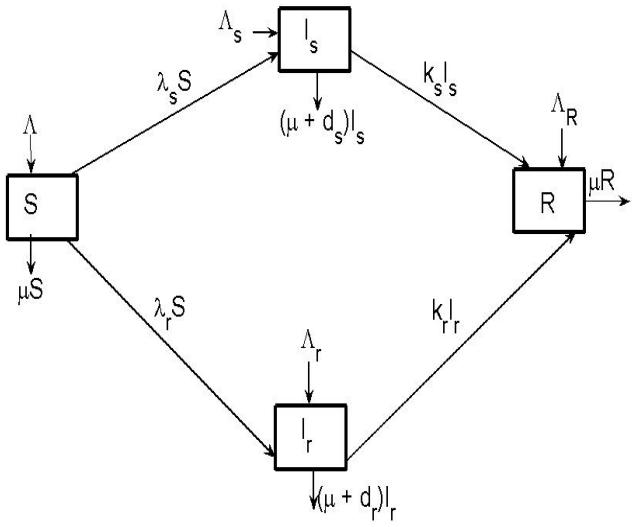


Figure 3.1: Flow chart illustrating the flow of individuals between the S, I_s, I_r, R classes.

3.2 Positivity of solutions

Since the model system (3.1.1) describes the influenza transmission dynamics among humans, we need to show that it is biological feasible. We have the following theorem:

Proposition 3.2.1. *If* $S(0) > 0, I_s(0) > 0, I_r(0) > 0, R(0) > 0$, *then the corresponding solution* $(S(t), I_s(t), I_r(t), R(t))$ *of system (3.1.1) is positive. Furthermore, the region*

$$D = \left\{ (S, I_s, I_r, R) \in \mathbb{R}^4_+ : S + I_s + I_r + R \leq \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu} \right\}$$

is positively invariant, that is, all solutions starting in D *will stay in* D *for all* $t \geq 0$. *We assume that* $\Lambda, \Lambda_s, \Lambda_r, \Lambda_R \geq 0$

Table 3.1: Description of parameters and variables for the model without control measures

Parameter/Variable	Description
S	Susceptible individuals.
I_s	Individuals infected with sensitive strain.
I_r	Individuals infected with resistant strain.
R	Recovery individuals.
Λ	Recruitment rate of susceptible individuals either through birth or immigration.
Λ_s	Recruitment rate of individuals infected with sensitive strain.
Λ_r	Recruitment rate of individuals infected with resistant strain.
Λ_R	Recruitment rate of recovered individuals.
μ	Natural death rate.
d_s	Disease induced death rate of individuals infected with sensitive strain.
d_r	Disease induced death rate of individuals infected with resistant strain.
k_s	Recovery rate of individuals infected with sensitive strain.
k_r	Recovery rate of individuals infected with resistant strain.
β_s	Transmission rate of individuals infected with sensitive strain.
β_r	Transmission rate of individuals infected with resistant strain.

Proof. Let $t_{\max}$ be the upper bound of the maximum interval corresponding to the solution $(S(t), I_s(t), I_r(t), R(t))$. To show that the solution is positive and bounded in $[0, +\infty[$, it is sufficient to show the positivity and boundedness result in $[0, t_{\max}[$.

Let

$$t_1 = sup\left\{0 \leq t < t_{\max} : S(\tau) > 0, I_s(\tau) > 0, I_r(\tau) > 0, R(\tau) > 0 \text{ for all } \tau \text{ in } [0, t]\right\}.$$

Since $S(0) > 0, I_s(0) > 0, I_r(0) > 0$ and $R(0) > 0$ are positive then $t_1 > 0$.

Using the variation of constants formula, we get

$$S(t_1) = \mathcal{U}(t_1, 0)S(0) + \frac{\Lambda}{N(t)} \int_0^{t_1} \mathcal{U}(t_1, z) > 0,$$

where $\mathcal{U}(t_1, z) = \exp\left(-\int_z^{t_1} (\mu + \lambda_s + \lambda_r)(\alpha)\, d\alpha\right)$.

Similarly, we can show that $I_s(t_1) > 0, I_r(t_1) > 0$ and $R(t_1) > 0$. This contra-

dicts the fact that at least one of the variables must be equal to zero at t_1. Hence $t_1 = t_{\max}$. This concludes the prove of positivity of solutions.

Next, we prove the boundedness of solutions. Assume the initial condition $X(0) = (S(0), I_s(0), I_r(0), R(0)) \in D$, then the corresponding solution of the model system (3.1.1) exists at all time $t < t_{\max}$. We need to show that any solution $X(t)$ with the initial condition in D is bounded and satisfies the inequality $N(t) \leq \frac{\Lambda}{\mu}$.

By adding together the equations of system (3.1.1) we get

$$\frac{dN(t)}{dt} = \Lambda + \Lambda_s + \Lambda_r + \Lambda_R - N(t) - (d_s I_s + d_r I_r), t < t_{\max}.$$

Since $I_s \geq 0$ and $I_r \geq 0$ on the region D

$$\Lambda + \Lambda_s + \Lambda_r + \Lambda_R + (\mu + d_s I_s + d_r I_r)N(t) \leq \frac{dN(t)}{dt} \leq \Lambda + \Lambda_s + \Lambda_r + \Lambda_R - \mu N(t) \tag{3.2.1}$$

for all $t < t_{\max}$.

Applying standard comparison theorem [6] we obtain

$$N(0)e^{-\mu t} + \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu + d_s + d_r}(1 - e^{-(\mu + d_s + d_r)t}) \leq N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu}(1 - e^{-\mu t}). \tag{3.2.2}$$

The first inequality shows that $N(t)$ is separated from the origin, the second one proves the invariance of D. In fact, if $N(0) \leq \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu}$, then $N(t) \leq \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu}$ for all $t \leq t_{\max}$. Therefore $t_{\max} = +\infty$ and $N(t) \leq \frac{\Lambda + \Lambda_s + \Lambda_r + \Lambda_R}{\mu}$ for all $t > 0$. □

3.3 Equilibrium points and reproduction number

An equilibrium point of the model system (3.1.1) satisfies the condition

$$\frac{dS}{dt} = \frac{dI_s}{dt} = \frac{dI_r}{dt} = \frac{dR}{dt} = 0,$$

that is, $S(t) = \hat{S}, I_s(t) = \hat{I}_s$, $I_r(t) = \hat{I}_r$ and $R(t) = \hat{R}$ for all $t \geq 0$, where $(\hat{S}, \hat{I}_s, \hat{I}_r, \hat{R})$ satisfies the following system

$$\begin{cases} \Lambda - (\mu + \hat{\lambda}_s + \hat{\lambda}_r)\hat{S} = 0 \\ \Lambda_s + \hat{\lambda}_s\hat{S} - \delta_s\hat{I}_s = 0 \\ \Lambda_r + \hat{\lambda}_r\hat{S} - \delta_r\hat{I}_r = 0 \\ \Lambda_R + k_s\hat{I}_s + k_r\hat{I}_r - \mu\hat{R} = 0 \end{cases} \tag{3.3.1}$$

3.3.1 Disease free equilibrium and basic reproduction number

At the disease free equilibrium, $\hat{I}_r$ and $\hat{I}_s$ are both equal to zero. Therefore

- If Λ_r or Λ_s is not equal to zero, the system (3.1.1) has no disease free equilibrium. In this case it is not easy to calculate the equilibrium points as it sufficient to tell whether people are infected through contacts with infected individuals from within the population or they are infected from other sources outside the population.
- If $\Lambda_r = \Lambda_s = 0$ and $\Lambda_R \geq 0$, then system (3.1.1) has a disease free equilibrium given by $E_0 = (\frac{\Lambda}{\mu}, 0, 0, \frac{\Lambda_R}{\mu})$. Notice that the presence of recovered

individuals at the equilibrium even though there is no disease. In fact, these individuals were not infected within this population, they were infected by an external source, recovered then moved into this population. If there is no immigration, there should be no recovered individuals at the equilibrium. This is the case when $\Lambda_R = 0$.

The value that R_0 takes can indicate the circumstances in which an epidemic can become endemic. In the influenza context, R_0 tells us, on average, the total number of people that each single infected individual will initiate to influenza virus during the period of infection in a completely susceptible population. The reproduction number is used to investigate the existence of equilibria for the dynamical system and also to discuss the stability of the disease free equilibrium. To determine R_0 for system (3.1.1) we follow a method in [22]. We consider the infection terms; I_s and I_r,

$$\begin{cases} \dfrac{dI_s}{dt} = \Lambda_s + \dfrac{\beta_s I_s}{N} S - (\mu + d_s + k_s) I_s, \\ \dfrac{dI_r}{dt} = \Lambda_r + \dfrac{\beta_r I_r}{N} S - (\mu + d_r + k_r) I_r. \end{cases} \tag{3.3.2}$$

Let F_n be the vector formed by new infection terms and V_r the vector constituted of the remaining transfer terms.

Let

$$F = \left[\frac{\partial F_{ni}(x_0)}{\partial x_j} \right]_{i,j},$$

and

$$V = \left[\frac{\partial V_{ri}(x_0)}{\partial x_j} \right]_{i,j} \text{ with } x_j = I_r \text{ or } I_s.$$

We have that

$$F_n = \begin{pmatrix} \Lambda_s + \beta_s I_s S/N \\ \\ \Lambda_r + \beta_r I_r S/N \end{pmatrix}$$

and

$$V_r = \begin{pmatrix} (\mu + d_s + k_s) I_s \\ \\ (\mu + d_r + k_r) I_r \end{pmatrix}.$$

Therefore the Jacobian Matrices of F_n and V_r at the DFE are as follows:

$$F(E_0) = \begin{pmatrix} \frac{\beta_s \Lambda}{\Lambda + \Lambda_R} & 0 \\ \\ 0 & \frac{\beta_r \Lambda}{\Lambda + \Lambda_R} \end{pmatrix}$$

and

$$V(E_0) = \begin{pmatrix} (\mu + d_s + k_s) & 0 \\ \\ 0 & (\mu + d_r + k_r) \end{pmatrix}.$$

Multiplying $F(E_0)$ by $V^{-1}(E_0)$ we get that

$$F(E_0)V^{-1}(E_0) = \begin{pmatrix} \frac{\Lambda \beta_s}{(\Lambda + \Lambda_R)(\mu + d_s + k_s)} & 0 \\ \\ 0 & \frac{\Lambda \beta_r}{(\Lambda + \Lambda_R)(\mu + d_r + k_r)} \end{pmatrix}.$$

Therefore the reproduction number is

$$R_0 = \max(R_{0s}, R_{0r})$$

where

$$R_{0s} = \frac{\Lambda \beta_s}{(\Lambda + \Lambda_R)(\mu + d_s + k_s)}$$

and

$$R_{0r} = \frac{\Lambda \beta_r}{(\Lambda + \Lambda_R)(\mu + d_r + k_r)}.$$

The biological interpretations of these quantities are as follows. Note that R_{0s} represents the number of new infections that one individual infected with the sensitive strain initiates in a completely susceptible population while R_{0r} represents the number of new infections that one individual infected with the sensitive strain initiates in a completely susceptible population.

3.4 Endemic equilibrium points

Let $\hat{E}_j = (\hat{S}, \hat{I}_s, \hat{I}_r, \hat{R})$, $j = r, s$ be any arbitrary endemic equilibrium point obtained by setting system (3.1.1) to zero, so that

$$\begin{cases} \Lambda - (\mu + \hat{\lambda}_s + \hat{\lambda}_r)\hat{S} = 0 \\ \Lambda_s + \hat{\lambda}_s\hat{S} - \delta_s\hat{I}_s = 0 \\ \Lambda_r + \hat{\lambda}_r\hat{S} - \delta_r\hat{I}_r = 0 \\ \Lambda_R + k_s\hat{I}_s + k_r\hat{I}_r - \mu\hat{R} = 0 \end{cases} \tag{3.4.1}$$

where $\delta_j = \mu + d_j + k_j$ and $\hat{\lambda}_j = \dfrac{\beta_j\hat{I}_j}{\hat{N}}$, $j = r, s$ with $\hat{N} = \hat{S} + \hat{I}_s + \hat{I}_r + \hat{R}$.
It is easy to see that when $\Lambda_s \neq 0$ (resp. $\Lambda_r \neq 0$), then $\hat{I}_s \neq 0$ (resp. $\hat{I}_r \neq 0$) suggesting that for the disease to be eradicated there should be no new infection from other sources outside the population.

From (3.4.1), we obtain

$$\begin{cases} \hat{S} = \dfrac{\Lambda}{\mu + \hat{\lambda}_s + \hat{\lambda}_r} \\ \hat{I}_s = \dfrac{\Lambda_s + \hat{\lambda}_s\hat{S}}{\delta_s} \\ \hat{I}_r = \dfrac{\Lambda_r + \hat{\lambda}_r\hat{S}}{\delta_r} \\ \hat{R} = \dfrac{\Lambda_R + k_s\hat{I}_s + k_r\hat{I}_r}{\mu} \end{cases} \tag{3.4.2}$$

Adding together, we obtain

$$\hat{N} = \frac{1}{\mu}\left[\Lambda_R + \Lambda_s\frac{\mu+k_s}{\delta_s} + \Lambda_r\frac{\mu+k_r}{\delta_r} + (\mu + \frac{\mu+k_s}{\delta_s}\hat{\lambda}_s + \frac{\mu+k_r}{\delta_r}\hat{\lambda}_r\hat{S}\right] \quad (3.4.3)$$

Let $\gamma_j = \dfrac{\mu+k_j}{\delta_j}$, $j = s, r$ then

$$\hat{N} = \frac{1}{\mu}\left[\Lambda_R + \Lambda_s\gamma_s + \Lambda_r\gamma_r + (\mu + \gamma_s\hat{\lambda}_s + \gamma_r\hat{\lambda}_r)\hat{S}\right] \quad (3.4.4)$$

On another hand, from the expressions of $\hat{\lambda}_j's$ we obtain $\hat{\lambda}_j\hat{N} = \beta_s\hat{I}_s$, $j = s, r$, which with the expressions of $\hat{N}$ and $\hat{I}_j's$, imply

$$\frac{1}{\mu}\left[\Gamma + (\mu + \gamma_s\hat{\lambda}_s + \gamma_r\hat{\lambda}_r)\hat{S}\right]\hat{\lambda}_j = \frac{\beta_j(\Lambda_j + \hat{\lambda}_j\hat{S})}{\delta_j}, \qquad j = s, r.$$

where $\Gamma = \Lambda_R + \Lambda_s\gamma_s + \Lambda_r\gamma_r$. Using the expression of $\hat{S}$, we have

$$\begin{cases} (\Delta_r\delta_s\hat{\lambda}_s - \mu\beta_s\Lambda_s)\hat{\lambda}_r + \Delta_s\delta_s\hat{\lambda}_s^2 + [(\Gamma+\Lambda)\,\delta_s - (\Lambda+\Lambda_s)\,\beta_s]\,\mu\hat{\lambda}_s - \mu^2\beta_s\Lambda_s = 0, \\ (\Delta_s\delta_r\hat{\lambda}_r - \mu\beta_r\Lambda_r)\hat{\lambda}_s + \Delta_r\delta_r\hat{\lambda}_r^2 + [(\Gamma+\Lambda)\,\delta_r - (\Lambda+\Lambda_r)\,\beta_r]\,\mu\hat{\lambda}_r - \mu^2\beta_r\Lambda_r = 0, \end{cases} \quad (3.4.5)$$

with $\Delta_j = \Gamma + \Lambda\gamma_j, j = r, s$.

To solve the (nonlinear) system (3.4.5) one can either solve the first (linear) equation of (3.4.5) for $\hat{\lambda}_r$ and substitute in the second equation. Alternatively, one can also solve the second (linear) equation of (3.4.5) for $\hat{\lambda}_s$ and substitute in the first equation. In both cases, the resulting equation is of 4^{th} order and is difficult to solve.

On that note, we consider a special case where $\Lambda_r = \Lambda_s = 0$, then we have $\Gamma = \Lambda_R$ and $\Delta_j = \Lambda_R + \Lambda\gamma_j$, so that equations (3.4.5) become

$$\begin{cases} \left[(\Lambda_R + \Lambda\gamma_r)\,\hat{\lambda}_r + (\Lambda_R + \Lambda\gamma_s)\,\hat{\lambda}_s + (\Lambda_R + \Lambda)\,(1 - R_{0s})\,\mu\right]\hat{\lambda}_s = 0 \\ \left[(\Lambda_R + \Lambda\gamma_s)\,\hat{\lambda}_s + (\Lambda_R + \Lambda\gamma_r)\,\hat{\lambda}_r + (\Lambda_R + \Lambda)\,(1 - R_{0r})\,\mu\right]\hat{\lambda}_r = 0. \end{cases} \quad (3.4.6)$$

Hence the following results are obtained.

1. If $R_{0s} < 1$ and $R_{0r} < 1$, then necessarily $\hat{\lambda}_s = \hat{\lambda}_r = 0$ giving the disease free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0, 0, \frac{\Lambda_R}{\mu})$.

2. If $R_{0s} < 1 < R_{0r}$, then from the first equation of (3.4.6) we obtain $\hat{\lambda}_s = 0$. This with the second equation of (3.4.6) imply that $\hat{\lambda}_r = 0$ (leading to E_0) or $\hat{\lambda}_r = \hat{\lambda}_{r0} := \dfrac{\mu\left(\Lambda_R + \Lambda\right)\left(R_{0r} - 1\right)}{\left(\Lambda_R + \Lambda\gamma_r\right)}$ leading the the endemic equilibrium $\hat{E}_r$ obtained by substituting $\hat{\lambda}_s = 0$ and $\hat{\lambda}_r = \hat{\lambda}_{r0}$ in (3.4.2. The resistant strain endemic equilibrium $\hat{E}_r$ is given by

$$\begin{cases} \hat{S} = \dfrac{\Lambda}{\mu + \hat{\lambda}_{r0}} \\ \hat{I}_s = 0 \\ \hat{I}_r = \dfrac{\hat{\lambda}_{r0}\hat{S}}{\delta_r} \\ \hat{R} = \dfrac{\Lambda_R + k_r\hat{I}_r}{\mu} \end{cases} \tag{3.4.7}$$

3. If $R_{0r} < 1 < R_{0s}$, then from the second equation of (3.4.6) we obtain $\hat{\lambda}_r = 0$. This with the first equation of (3.4.6) imply that $\hat{\lambda}_s = 0$ (leading to E_0) or $\hat{\lambda}_s = \hat{\lambda}_{s0} := \dfrac{\mu\left(\Lambda_R + \Lambda\right)\left(R_{0s} - 1\right)}{\left(\Lambda_R + \Lambda\gamma_s\right)}$ leading the the endemic equilibrium $\hat{E}_s$ obtained by substituting $\hat{\lambda}_r = 0$ and $\hat{\lambda}_s = \hat{\lambda}_{s0}$ in (3.4.2). The sensitive strain endemic equilibrium $\hat{E}_s$ is given by

$$\begin{cases} \hat{S} = \dfrac{\Lambda}{\mu + \hat{\lambda}_{s0}} \\ \hat{I}_s = \dfrac{\hat{\lambda}_{s0}\hat{S}}{\delta_s} \\ \hat{I}_r = 0 \\ \hat{R} = \dfrac{\Lambda_R + k_s\hat{I}_s}{\mu} \end{cases} \tag{3.4.8}$$

4. If $R_{0r} > 1$ and $R_{0s} > 1$, then either

   i. $\hat{\lambda}_s = \hat{\lambda}_r = 0$, giving the disease free endemic equilibrium E_0, or

ii. $\hat{\lambda}_s = 0$ and $\hat{\lambda}_r \neq 0$, giving the resistant strain endemic equilibrium $\hat{E}_r$, or

iii. $\hat{\lambda}_r = 0$ and $\hat{\lambda}_s \neq 0$, giving the sensitive strain endemic equilibrium $\hat{E}_s$, or

iv. $\hat{\lambda}_r \neq 0$ and $\hat{\lambda}_s \neq 0$. In this case we have the following system

$$\begin{cases} (\Lambda_R + \Lambda\gamma_r)\,\hat{\lambda}_r + (\Lambda_R + \Lambda\gamma_s)\,\hat{\lambda}_s + (\Lambda_R + \Lambda)\,(1 - R_{0s})\,\mu = 0 \\ (\Lambda_R + \Lambda\gamma_r)\,\hat{\lambda}_r + (\Lambda_R + \Lambda\gamma_s)\,\hat{\lambda}_s + (\Lambda_R + \Lambda)\,(1 - R_{0r})\,\mu = 0. \end{cases}$$

This implies that $R_{0s} = R_{0r}$ $(= R_0)$. In this case we have two cases

Note that this are sub-cases of cases from **i** to **iv**.

a. If $R_{0r} \neq R_{0s}$, then there is no endemic equilibria.

b. If $R_{0r} = R_{0s}$, then

$$\hat{\lambda}_r = \hat{\lambda}_{0r} - \frac{\hat{\lambda}_{0r}}{\hat{\lambda}_{0s}}\hat{\lambda}_s,$$

In this case system (3.1.1) has a family of endemic equilibria given by

$$\begin{cases} \hat{S} = \dfrac{\Lambda}{\mu + \hat{\lambda}_s + \hat{\lambda}_{r0} - \frac{\hat{\lambda}_{r0}}{\hat{\lambda}_{s0}}\hat{\lambda}_s} \\ \hat{I}_s = \dfrac{\hat{\lambda}_s \hat{S}}{\delta_s} \\ \hat{I}_r = \dfrac{\left(\hat{\lambda}_{r0} - \frac{\hat{\lambda}_{0r}}{\hat{\lambda}_{s0}}\hat{\lambda}_s\right)\hat{S}}{\delta_r} \\ \hat{R} = \dfrac{\Lambda_R + k_s\hat{I}_s + k_r\hat{I}_r}{\mu} \end{cases} \tag{3.4.9}$$

where $0 < \hat{\lambda}_s < \hat{\lambda}_{s0}$, is arbitrary.

If $\lambda_r \neq 0$ and $\lambda_s \neq 0$ then system (3.1.1) has endemic equilibria. But if $\lambda_r = 0$ and $\lambda_s = 0$ then system (3.1.1) has disease free equilibrium.

The existence of the equilibria is given in the following proposition, where we assume that $\lambda_s, \Lambda_r = 0$.

Proposition 3.4.1. *1. If $R_{0s} < 1$ and $R_{0r} < 1$, then system (3.1.1) has only one equilibrium point, the disease free equilibrium point, E_0.*

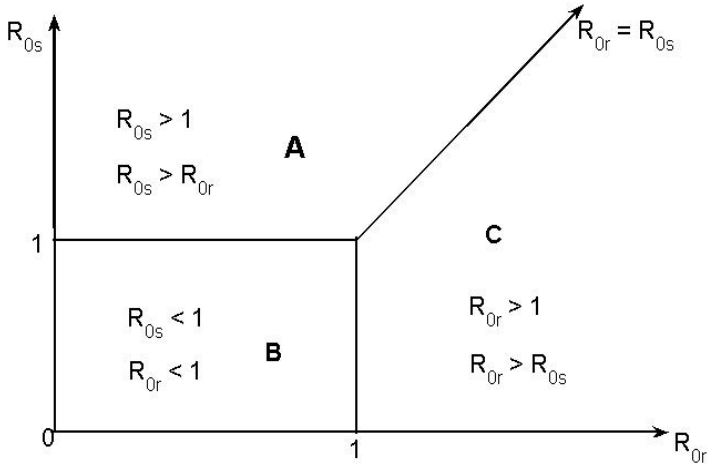
2. If $R_{0s} < 1 < R_{0r}$, then in addition to E_0 system (3.1.1) has another equilibrium point, the equilibrium point, $\hat{E}_r$.

3. If $R_{0r} < 1 < R_{0s}$, then in addition to E_0 system (3.1.1) has another equilibrium point, the equilibrium point, $\hat{E}_s$.

4. If $R_{0r} > 1$ and $R_{0s} > 1$, and $R_{0r} \neq R_{0s}$, then system (3.1.1) has three equilibrium points, $E_0, \hat{E}_s$ and $\hat{E}_r$.

5. If $R_{0r} > 1$ and $R_{0s} > 1$, and $R_{0r} = R_{0s}$, then in addition to $E_0, \hat{E}_s$ and $\hat{E}_r$, system (3.1.1) has a family of equilibrium points given by (3.4.9).

Figure 3.2: Existence of equilibrium points.



From figure (3.2) we have the following summary of existence of the equilibria described in proposition (3.4.1).

- In region A the equilibrium point with the sensitive strain, $\hat{E}_s$, exists
- In region C the equilibrium point with the sensitive strain, $\hat{E}_r$, exists and
- In region B the DFE, E_0 exists.

3.5 Stability Analysis of the DFE

The Jacobian Matrix of system (3.1.1) at the disease free equilibrium, $E_0 = (\frac{\Lambda}{\mu}, 0, 0, \frac{\Lambda_R}{\mu})$ is given by

$$J(E_0) = \begin{pmatrix} -\mu & -\frac{\beta_s\Lambda}{\Lambda+\Lambda_R} & -\frac{\beta_r\Lambda}{\Lambda+\Lambda_R} & 0 \\ 0 & \frac{\beta_s\Lambda}{\Lambda+\Lambda_R} - (\mu + d_s + k_s) & 0 & 0 \\ 0 & 0 & \frac{\beta_r\Lambda}{\Lambda+\Lambda_R} - (\mu + d_r + k_r) & 0 \\ 0 & k_s & k_r & -\mu \end{pmatrix}$$

and its characteristics polynomial is given by

$$P(x) = \frac{1}{(\Lambda + \Lambda_R)^2}(\mu+x)^2(\beta_s\Lambda+\delta_s\Lambda+\Lambda_R x+\Lambda x+\delta_s\Lambda_R)(\Lambda x+\Lambda_R x-\beta_r\Lambda+\Lambda\delta_r+\delta_r\Lambda_R).$$

Solving $P(x) = 0$, we get $x_1 = -\mu$,

$$\begin{aligned} x_2 &= \frac{\Lambda\beta_r}{\Lambda + \Lambda_R} - \delta_r \\ &= \delta_r(R_{0r} - 1). \end{aligned}$$

$$\begin{aligned} x_3 &= \frac{\Lambda\beta_s}{\Lambda + \Lambda_R} - \delta_s \\ &= \delta_s(R_{0s} - 1). \end{aligned}$$

It is clear that if $R_{0r} < 1$ and $R_{0s} < 1$, then all the eigenvalues are negative, implying that E_0 is locally asymptotically stable. Otherwise, at least one of the eigenvalues is positive, implying that E_0 is unstable. As a result we have the following proposition.

Proposition 3.5.1. *If $R_{0r} < 1$ and $R_{0s} < 1$, then E_0 is locally asymptotically stable. Otherwise, E_0 is unstable.*

3.6 Stability analysis of the endemic equilibria

Proposition 3.6.1. *If $R_{0r} > 1$ and $R_{0r} > R_{0s}$, then the endemic equilibrium point of system (3.1.1), $\hat{E}_r$ is locally asymptotically stable.*

Proof. The eigenvalues of the Jacobian Matrix of system (3.1.1) at the endemic equilibrium $\hat{E}_r$ are given by

$$\begin{aligned} x_1 &= -\mu < 0\text{and} \\ x_2 &= \frac{(R_{0s} - R_{0r})\delta_s}{R_{0r}} \end{aligned}$$

which is negative if and only if $R_{0r} > R_{0s}$. The other two eigenvalues are given by the roots of the following quadratic equation

$$a_2x^2 + a_1x + a_0 = 0, \tag{3.6.1}$$

where

$$\begin{cases} a_2 = (\Lambda_R\delta_r + \Lambda(\mu + k_r))R_{or} \\ a_1 = \mu R_{or}(\Lambda(\mu + k_r) + \Lambda\delta_r(R_{0r} - 1) + \Lambda_R\delta_r R_{or})) \\ a_0 = \mu\delta_r(R_{or} - 1)(\Lambda(\mu + k_r) + \Lambda\delta_r(R_{or} - 1) + \Lambda_R\delta_r R_{or}). \end{cases}$$

If $R_{0r} > 1$ then the quadratic equation (3.6.1) has positive coefficients which, by Routh-Hurwitz, criterion implies that the other two eigenvalues have negative real parts. Thus, if $R_{0s} < R_{0r}$ and $R_{0r} > 1$, then $\hat{E}_r$ is locally asymptotically stable. □

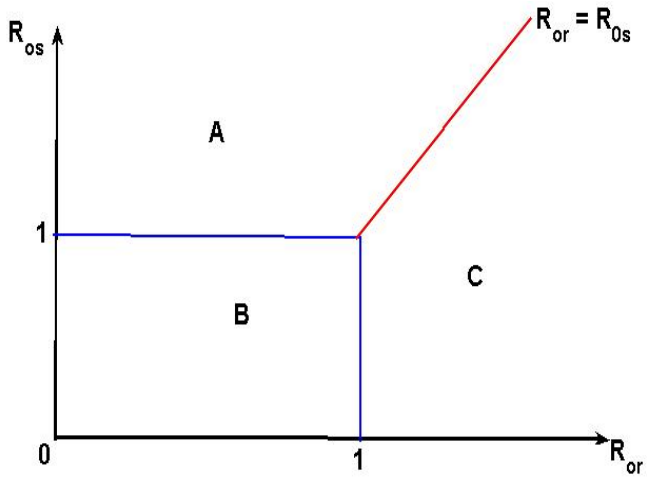


Figure 3.3: Bifurcation diagram in the (R_{0r}, R_{0s}) plane for the following cases: $R_{0s} > 1$ and $R_{0s} > R_{0r}$ (Region A), $R_{0s} < 1$ and $R_{0r} < 1$ (Region B), $R_{0r} > 1$ and $R_{0r} > R_{0s}$ (Region C).

Proposition 3.6.2. *If $R_s > 1$ and $R_{0s} > R_{0r}$, then the endemic equilibrium, of system (3.1.1), $\hat{E}_s$ is locally asymptotically stable.*

The proof is similar to the one for $\hat{E}_r$.

The stability for each equilibrium point is summarized in the bifurcation diagram (3.3).

From bifurcation diagram (3.3) we observe that

- In region A, sensitive strain equilibrium point, E_s is locally asymptotically stable.
- In region B, DFE, E_0 is locally asymptotically stable.
- In region C, resistant strain equilibrium point, E_r is locally asymptotically stable.

3.7 Numerical simulations and discussions

In this section, we present some numerical simulation results which illustrate the effects of not controlling the disease. The model (3.1.1) is simulated using Python with the parameter values in table (3.2) and the initial conditions $S(0) = 800, I_s = 10, I_r = 0, R(0) = 0$. Note that due to unavailability of data we have used the parameters values from [18]. We consider the transmission parameters β_s and β_r as free (bifurcation) parameters so that $R_{0s} < 1$ (resp. $R_{0r} < 1$) if and only if $\beta_s < \beta_s^*$ (resp. $\beta_r < \beta_r^*$) where

$$\begin{cases} \beta_s^* = \dfrac{(\Lambda + \Lambda_R)(\mu + d_s + k_s)}{\Lambda}, \\ \beta_r^* = \dfrac{(\Lambda + \Lambda_R)(\mu + d_r + k_r)}{\Lambda}. \end{cases} \tag{3.7.1}$$

Table 3.2: Parameter values used in the simulations for system 3.1.1 taken from [18]. the unit of all rates is day^{-1}.

Parameter	Parameter values
$\Lambda, \Lambda_s, \Lambda_r, \Lambda_R$	9000
μ	0.00005
β_s	0.2835
β_r	0.2835
d_r	$0.007 - 0.45$ [2]
d_s	$0.007 - 0.45$ [2]
k_r	0.1667
k_s	0.1667

When $R_0 < 1$, then the population dynamics of infected individuals are shown in Figure (3.4). We observe that both resistant and sensitive strains die out. This confirms the asymptotic stability result of the DFE.

When $R_{0r} > 1$ and $R_{0r} > R_{0s}$, the population dynamics of infected individuals are represented in Figure (3.5). We observe that the number of individuals infected with the resistant strain increases and reaches the equilibrium point while that of individuals infected with the sensitive strain decreases and reaches zero. This confirms the local asymptotic stability result of E_r.

When $R_{0s} > 1$ and $R_{0s} > R_{0r}$ the population dynamics of infected individuals are represented in Figure (3.6). We observe that the number of individuals infected with the sensitive strain increases and reaches the equilibrium point while that of individuals infected with the resistant strain decreases and reaches zero. In this case the equilibrium point for sensitive strain is locally asymptotically stable. This confirms the local asymptotic stability result of $\hat{E}_s$.

From Figure (3.7) we observe the population dynamics of the resistant strain

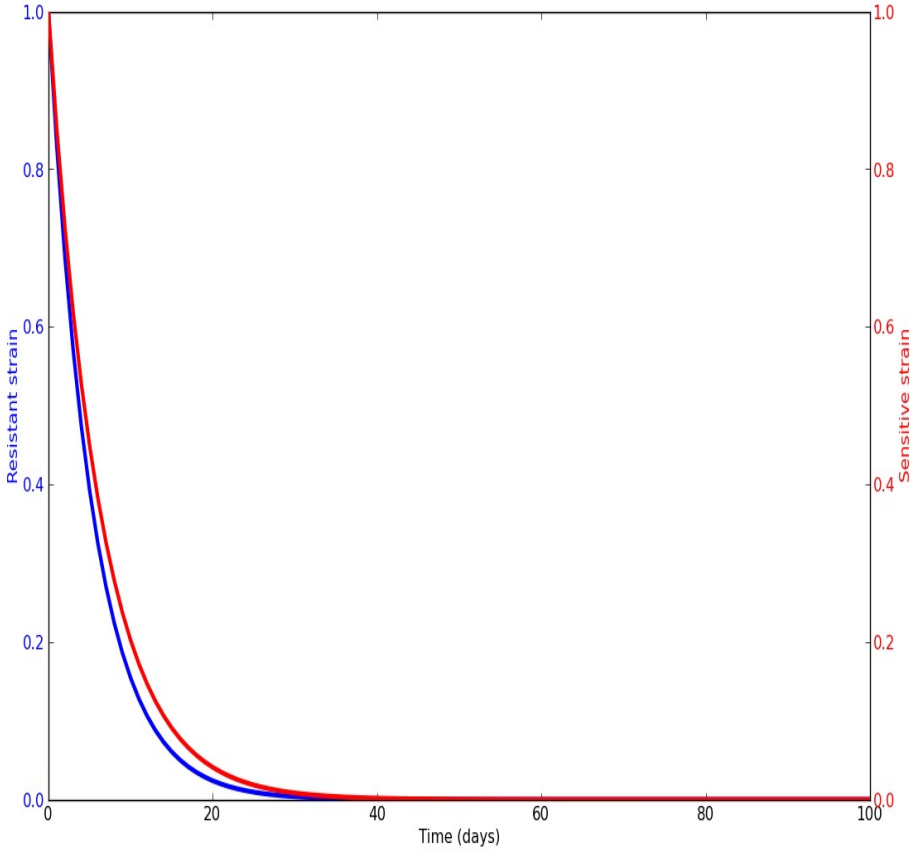


Figure 3.4: Population dynamics for influenza model without control measures when $R_0 < 1$.

when taking into consideration different disease induced death rates. We observe that the number of individuals infected with the resistant strain reaches the peak on the 95^{th} day and approximately 300000 individuals die due to the disease. After that it declines and have another peak lower than the first one on the 195^{th} day and also on the 199^{th} day and becomes stable after the 200^{th} day. This shows that without the control measures the mortality rate due to the disease will increase dramatically. So it is important to implement control measures such as treatment and vaccination.

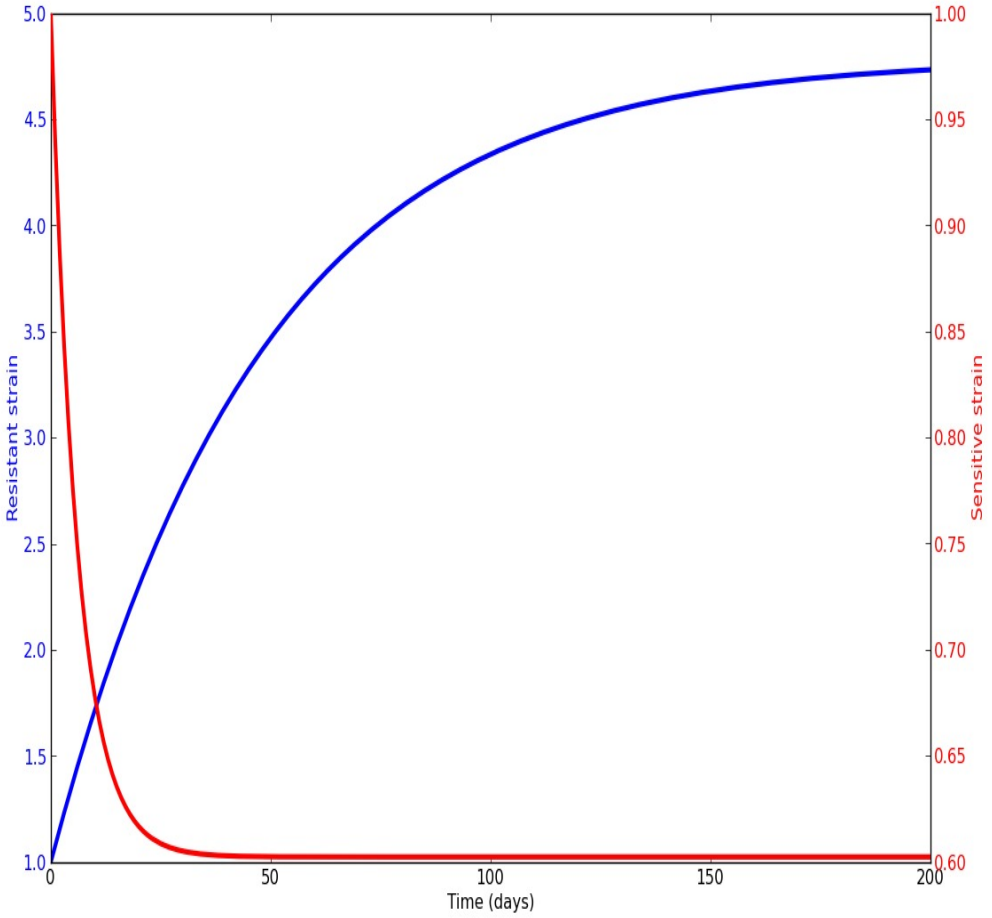


Figure 3.5: Population dynamics for influenza model without control measures when $R_{0r} > 1$ and $R_{0r} > R_{0s}$.

It is clear that when $R_{0s} > 1$ or $R_{0r} > 1$, (interventions such as treatment and vaccination are not implemented) the disease will just continue to spread. In the next chapter we shall demonstrate the impact of antiviral treatment and vaccination in eradicating the spread of influenza.

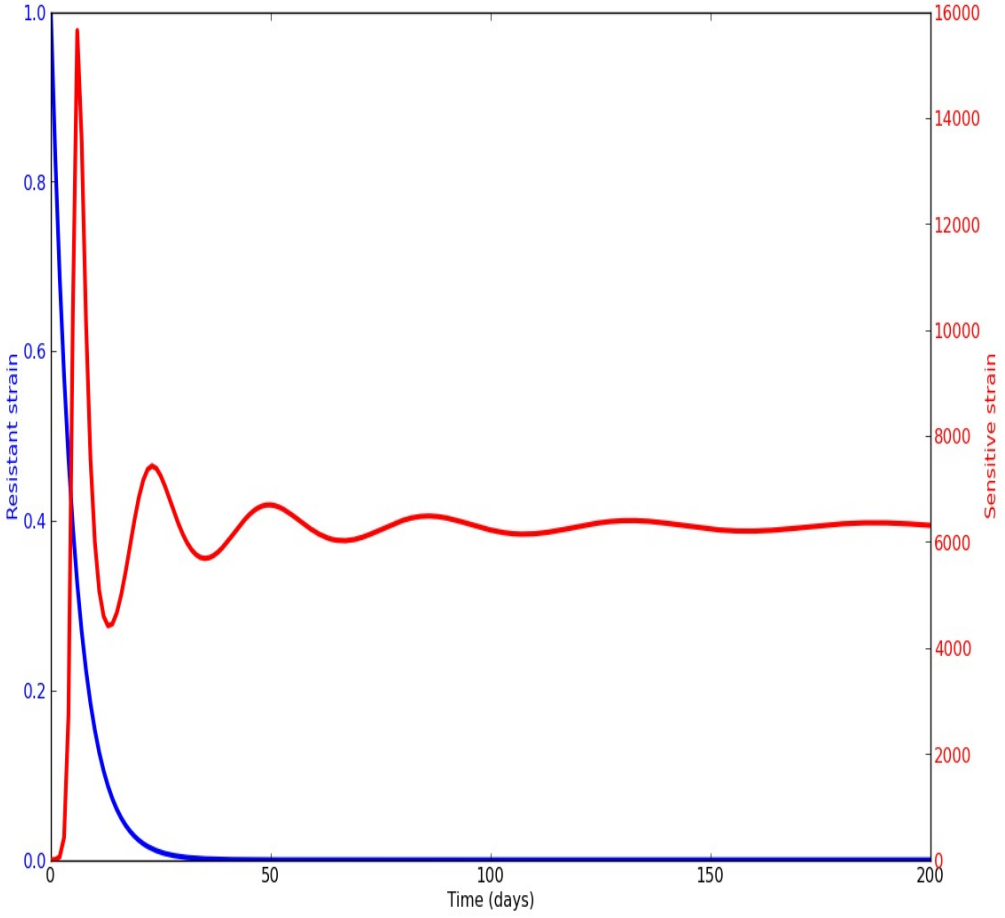


Figure 3.6: Population dynamics for influenza model without control measures when $R_{0s} > 1$ and $R_{0s} > R_{0r}$.

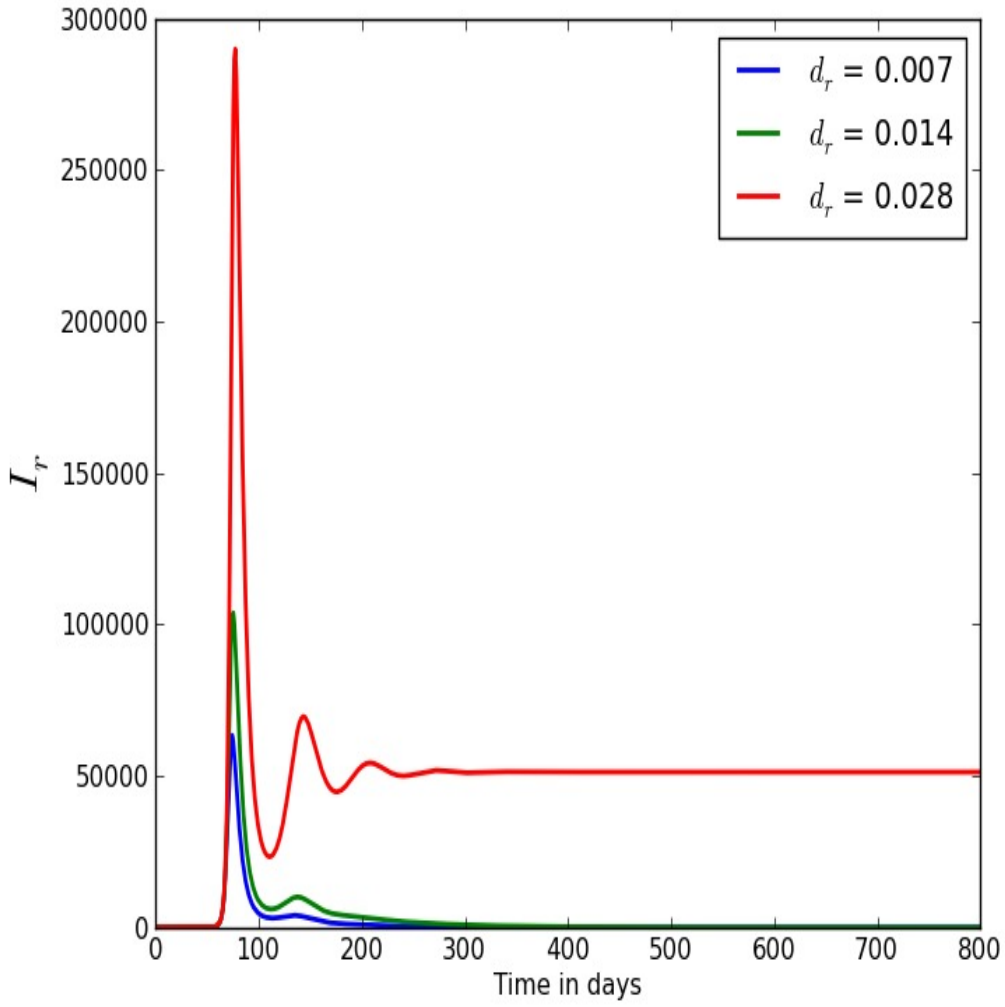


Figure 3.7: Population dynamics for influenza model without control measures considering the different disease induced death rates, d_r.

Chapter 4

Influenza model with vaccination and antiviral treatment

4.1 Model formulation

We extend the model in chapter 3 to incorporate control measures such as treatment and vaccination. For this the class for the sensitive strain is divided into two classes: I_{su} for untreated individuals and I_{st} for treated ones. To account for vaccination, we distinguish between susceptible individuals who are vaccinated, V and those who are not, S. With this, the total population becomes

$$N = S + V + I_{su} + I_{st} + I_r + R.$$

Susceptible individuals are assumed to be vaccinated at a per-capita rate ν with immunity waning (immunity decreases gradually) at per-capita rate σ. A fraction f of individuals infected with the sensitive strain receive treatment.

The transmission rate for an individual who received treatment will be reduced by a factor δ.

Table 4.1: Description of parameters and variables for the model with control measures

Parameter	Description
I_{su}	Individuals infected with the sensitive strain and untreated.
I_{st}	Individuals infected with the sensitive strain an treated.
V	Vaccinated individuals.
ν	Rate at which susceptible individuals are vaccinated.
σ	Rate at which individuals lose vaccine-induced immunity.
ω	Rate at which individuals lose immunity acquired by infection.
δ	Reduction factor in infectiousness due to the antiviral treatment.
f	Fraction of new infected individuals who are treated.
k_{su}	Recovery rate of individuals infected with the sensitive strain and untreated.
k_{st}	Recovery rate of individuals infected with the sensitive strain and treated.
d_{su}	Death rate due to sensitive untreated strain.

Susceptible population is increased through recruitment of individuals either by immigration or birth at the rate Λ. Susceptible individuals exit the compartment S and enter the following compartments: V for vaccinated individuals (at a rate ν), the class of individuals infected with the sensitive strain who are not treated I_{su} (at a rate $(1-f)\lambda_s$), the individuals infected with the sensitive strain being treated I_{st} (at a rate $f\lambda_s$) and individuals infected with the resistant strain I_r (at a rate λ_r). There is a possibility that susceptible individuals die due to natural causes at a rate μ.

Vaccinated individuals may die due to natural causes at a rate μ and there is a possibility that they revert to the susceptible class S at a rate σ. Untreated individuals can either die due to natural causes at a rate μ or due to influenza

at a rate d_{su}. Treated individuals can either die due to natural causes at a rate μ or progress to a recovered class R at a rate k_{st}. Individuals infected with the resistant strain can recover naturally at a rate k_r, they can also die due to influenza at a rate d_r or due to natural causes at a rate μ. Recovered individuals can loose immunity at a rate ω or die due to natural causes at a rate μ.

The model diagram describing the flows between the model's compartments is given in figure (4.1).

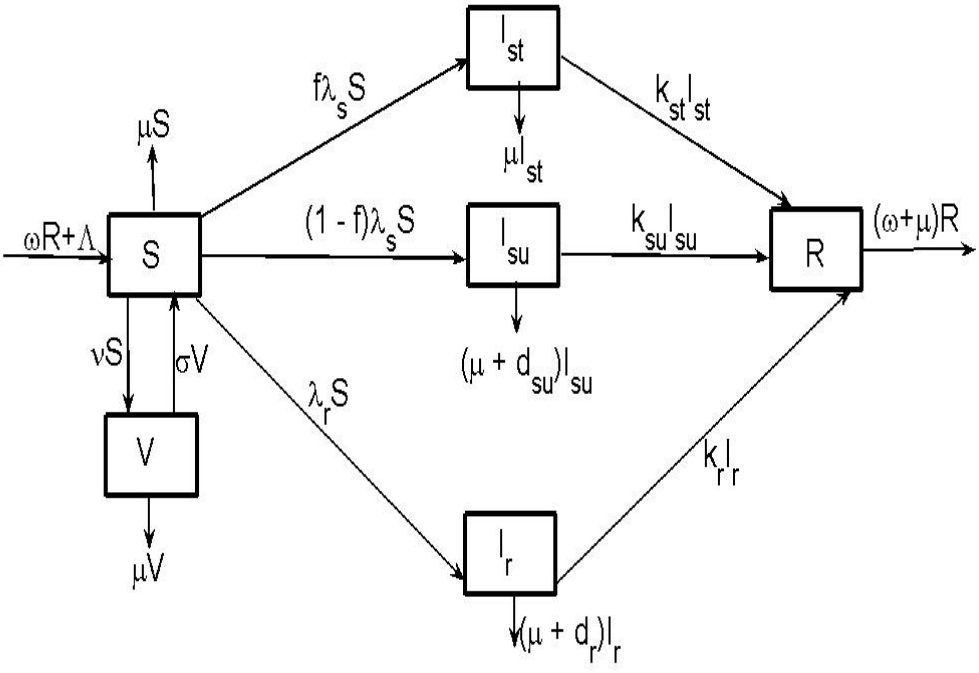


Figure 4.1: The model diagram of influenza with vaccination and antiviral treatment where $\lambda_s = \dfrac{\beta_s I_{su} + \delta\beta_s I_{st}}{N}$ and $\lambda_r = \dfrac{\beta_r I_r}{N}$.

Notice that in this model we ignore the recruitment rates into the recovered and infected classes. The model's parameters and variables related to treatment and vaccination are described in table 4.1. The remaining parameters and variables are the same as in Chapter 3. Based on the above model's diagram, we have the following system of differential equations:

$$\begin{cases} \frac{dS}{dt} = \Lambda - (\mu+\nu)S - \lambda_s S - \lambda_r S + \omega R + \sigma V, \\ \frac{dV}{dt} = \nu S - (\sigma+\mu)V, \\ \frac{dI_{su}}{dt} = (1-f)\lambda_s S - (\mu+d_{su})I_{su} - k_{su}I_{su}, \\ \frac{dI_{st}}{dt} = f\lambda_s S - k_{st}I_{st} - \mu I_{st}, \\ \frac{dI_r}{dt} = \lambda_r S - (\mu+d_r)I_r - k_r I_r, \\ \frac{dR}{dt} = k_{su}I_{su} + k_{st}I_{st} + k_r I_r - (\mu+\omega)R. \end{cases} \tag{4.1.1}$$

4.1.1 Positivity and boundedness of solutions

Since influenza model monitors the dynamics of the human population it is important that all the model variables stay positive at all times. We introduce a region of feasibility Ω.

$$\Omega = \left\{ (S, V, I_{su}, I_{st}, I_r, R) \in \mathbb{R}^6_+ : S + V + I_{su} + I_{st} + I_r + R \leq \frac{\Lambda}{\mu} \right\}.$$

Proposition 4.1.1. *Let $S(0) \geq 0, V(0) \geq 0, I_{su}(0) \geq 0, I_{st}(0) \geq 0, I_r(0) \geq 0, R(0) \geq 0$ and assume that $\Lambda > 0$. Then the corresponding solution $S, V, I_{su}, I_{st}, I_r, R$ of system (4.1.1) is positive. Furthermore, the region Ω is positively invariant that is all solutions starting in Ω remain in Ω for all time $t \geq 0$.*

(The proof is similar to the one in Chapter 3)

4.2 Equilibrium points and reproduction number

4.2.1 Equilibrium points

To determine the equilibrium points of the system (4.1.1) we need to solve simultaneously the following equations

$$\begin{cases} 0 = \Lambda - (\mu+\nu)S - \lambda_s S - \lambda_r S + \omega R + \sigma V, \\ 0 = \nu S - (\sigma+\mu)V, \\ 0 = (1-f)\lambda_s S - (\mu + d_{su})I_{su} - k_{su}I_{su}, \\ 0 = f\lambda_s S - k_{st}I_{st} - \mu I_{st}, \\ 0 = \lambda_r S - (\mu + d_r)I_r - k_r I_r, \\ 0 = k_{su}I_{su} + k_{st}I_{st} + k_r I_r - (\mu+\omega)R. \end{cases} \tag{4.2.1}$$

4.2.2 Disease free equilibrium

In the absence of influenza infection, system (4.2.1) becomes

$$\begin{cases} 0 = \Lambda - (\mu+\nu)S + \sigma V, \\ 0 = \nu S - (\sigma+\mu)V. \end{cases} \tag{4.2.2}$$

By solving system (4.2.2) we obtain the disease free equilibrium given by

$$E_0 = (S_0, V_0, 0, 0, 0, 0)$$

where

$$S_0 = \frac{(\sigma+\mu)\Lambda}{\mu(\sigma+\mu+\nu)},$$
$$V_0 = \frac{\nu\Lambda}{\mu(\sigma+\mu+\nu)}.$$

representing the numbers of susceptible individuals and vaccinated individuals, respectively, in the absence of influenza infection.

To find the other equilibria, we first determine the reproduction number, R_{0C} of the dynamical system (4.1.1) (The subscript C denotes the combined interventions, treatment and vaccination). For this we follow the same method as in chapter 3. We consider the infection terms: I_{su}, I_{st}, and I_r. After similar algebraic procedure as in chapter 3 we obtain

$$R_{0C} = \max(R_{0sC}, R_{0rC}),$$

where

$$\begin{cases} R_{0sC} = \dfrac{\sigma+\mu}{\sigma+\mu+\nu} R_{0s}, \\ R_{0rC} = \dfrac{\sigma+\mu}{\sigma+\mu+\nu} R_{0r} \end{cases} \tag{4.2.3}$$

with

$$\begin{cases} R_{0s} = (1-f)R_{0su} + fR_{0st} \\ R_{0su} = \dfrac{\beta_s}{\mu+k_{su}+d_{su}}, \\ R_{0st} = \dfrac{\beta_s\delta}{\mu+k_{st}}, \\ R_{0r} = \dfrac{\beta_r}{\mu+k_r+d_r}. \end{cases} \tag{4.2.4}$$

The biological interpretations of these quantities are as follows:
The quantities R_{0st} and R_{0su} represent the number of secondary sensitive cases produced by a treated and untreated sensitive case, respectively, during the period of infection in a susceptible population.

Each sensitive case may either receive treatment with probability f or remain untreated with probability $1-f$. The quantity R_{0sC} represents the number of secondary sensitive cases produced by a typical sensitive case during the

period of infection in a population where control measures (vaccination and treatment) are implemented.

Similarly, the quantity R_{0r} represents the number of secondary resistant cases produced by a resistant case during the period of infection in a completely susceptible population. Thus, the quantity R_{0rC} (where r is for resistant and C is for control) represents the number of secondary resistant cases produced by a typical resistant case, that is, the control reproduction number for the resistant strain, during the period of infection in a population.

By [22], we state the local stability of the DFE in the following theorem.

Theorem 4.2.1. *The DFE, E_0 is locally asymptotically stable if and only if $R_{0C} < 1$.*

4.2.3 Endemic equilibrium points

In the presence of treatment we have system (4.2.1). Solving system (4.2.1) simultaneously we get

$$\begin{cases} \hat{V} = \dfrac{\nu \hat{S}}{\sigma + \mu}, \\ \hat{I_{su}} = \dfrac{(1-f)\hat{\lambda}_s \hat{S}}{\mu + d_{su} + k_{su}} \\ \hat{I_{st}} = \dfrac{f\hat{\lambda}_s \hat{S}}{k_{st} + \mu} \\ \hat{I_r} = \dfrac{\hat{\lambda}_r \hat{S}}{\mu + d_r + k_r} \\ \hat{R} = \dfrac{k_{su}\hat{I_{su}} + k_{st}\hat{I_{st}} + k_r \hat{I_r}}{\mu + \omega}, \end{cases} \tag{4.2.5}$$

where

$$\hat{S} = \frac{\Lambda\left(k_{st}+\mu\right)\left(\mu + d_{su} + k_{su}\right)\left(\mu + d_r + k_r\right)\left(\mu+\omega\right)\left(\sigma+\mu\right)}{A + A_r\hat{\lambda}_r + A_s\hat{\lambda}_s} \tag{4.2.6}$$

with

$$\begin{cases} A = \mu\left(k_{st}+\mu\right)\left(\mu+d_{su}+k_{su}\right)\left(\mu+d_r+k_r\right)\left(\mu+\omega\right)\left(\mu+\nu+\sigma\right), \\ A_r = \left(k_{st}+\mu\right)\left(\mu+d_{su}+k_{su}\right)\left(\sigma+\mu\right)\left(\mu^2+\mu d_r+\mu\omega+\mu k_r+d_r\omega\right) \\ A_s = \left(\mu+d_r+k_r\right)\left(\sigma+\mu\right)\left[\begin{array}{l}\omega\left(\mu^2+\mu d_{su}+\mu k_{su}f+\left(1-f\right)\mu k_{st}+\left(1-f\right)k_{st}d_{su}\right) \\ +\mu\left(k_{st}+\mu\right)\left(\mu+d_{su}+k_{su}\right)\end{array}\right]. \end{cases}$$

Adding together the right hand side of (4.2.5), we obtain

$$\hat{N} = \hat{S}\left[\frac{\sigma+\mu+\nu}{\sigma+\mu} + \left(\frac{(1-f)(\mu+\omega+k_{su})}{(\mu+d_{su}+k_{su})(\mu+\omega)} + \frac{f(\mu+\omega+k_{st})}{(k_{st}+\mu)(\mu+\omega)}\right)\hat{\lambda}_s + \frac{\mu+\omega+k_r}{(\mu+k_r+d_r)(\mu+\omega)}\hat{\lambda}_r\right].$$

Substituting the expression of $\hat{N}$ into $\hat{\lambda}_s = \dfrac{\beta_s\hat{I}_{su}+\delta\beta_s\hat{I}_{st}}{\hat{N}}$ and $\hat{\lambda}_r = \dfrac{\beta_r\hat{I}_r}{\hat{N}}$, we obtain the solutions of the following system

$$\begin{cases} \left[\gamma_r\hat{\lambda}_r+\gamma_s\hat{\lambda}_s+\left(1-R_{0rC}\right)\right]\hat{\lambda}_r = 0 \\ \left[\gamma_r\hat{\lambda}_r+\gamma_s\hat{\lambda}_s+\left(1-R_{0sC}\right)\right]\hat{\lambda}_s = 0 \end{cases} \tag{4.2.7}$$

where

$$\gamma_r = \frac{\mu+\omega+k_r}{\left(\mu+\omega\right)\left(\mu+d_r+k_r\right)}\left[\frac{\left(\mu+\sigma\right)}{\sigma+\mu+\nu}\right]$$
$$\gamma_s = \frac{\left(\mu+k_{su}\right)\left(\mu+k_{st}\right)+f\left(d_{su}\left(k_{st}+\mu+\omega\right)+k_{su}\omega\right)+\mu\omega+\left(1-f\right)k_{st}\omega}{\left(k_{st}+\mu\right)\left(\mu+d_{su}+k_{su}\right)\left(\mu+\omega\right)}\left[\frac{\left(\mu+\sigma\right)}{\sigma+\mu+\nu}\right].$$

Thus

1. If $R_{0rC} < 1$ and $R_{0sC} < 1$, then necessarily $\hat{\lambda}_s = \hat{\lambda}_r = 0$. Hence we have the DFE, $E_0 = (S_0, V_0, 0, 0, 0, 0)$.

2. If $R_{0rC} > 1$ and $R_{0sC} < 1$, then from the second equation of system (4.2.1) we obtain $\hat{\lambda}_s = 0$. This, together with the first equation of (4.2.1) imply that $\hat{\lambda}_r = 0$ (leading to DFE) or

$$\hat{\lambda_r} =: \hat{\lambda_{0r}} = \frac{(R_{0rC}-1)(\sigma+\mu+\nu)(\mu+d_r+k_r)(\mu+\omega)}{(\sigma+\mu)(\mu+\omega+k_r)}.$$

Substituting $\hat{\lambda_s} = 0$ and $\hat{\lambda_r} = \hat{\lambda_{0r}}$, into system (4.2.5), we obtain the endemic equilibrium $\hat{E}_r$ given by

$$\begin{cases} \hat{V} = \dfrac{\nu \hat{S}}{\sigma + \mu}, \\ \hat{I_{su}} = \hat{I_{st}} = 0, \\ \hat{I}_r = \dfrac{\hat{\lambda_{0r}} \hat{S}}{\mu + d_r + k_r} \\ \hat{R} = \dfrac{k_r \hat{I}_r}{\mu + \omega}, \end{cases} \tag{4.2.8}$$

where $\hat{S}$, is defined in equation (4.2.6).

3. If $R_{0rC} < 1$ and $R_{0sC} > 1$, then from the first equation of system (4.2.1) we obtain $\hat{\lambda}_s = 0$, this together with the second equation of (4.2.1) imply that $\hat{\lambda}_s = 0$ (leading to DFE) or

$$\hat{\lambda_{0s}} = \frac{(R_{0sC} - 1)(\mu + d_{su} + k_{su})(\mu + \omega)(\mu + k_{st})}{(1 - f)(\mu + \omega + k_{su})(\mu + k_{st})(\mu + \omega) + f(\mu + d_{su} + k_{su})(\mu + \omega + k_{st})}.$$

Substituting $\hat{\lambda_r} = 0$ and $\hat{\lambda_s} = \hat{\lambda_{0s}}$ into system (4.2.5) we obtain the endemic equilibrium $\hat{E}_s$ given by

$$\begin{cases} \hat{V} = \dfrac{\nu \hat{S}}{\sigma + \mu}, \\ \hat{I_{su}} = \dfrac{(1 - f)\hat{\lambda_{0s}} \hat{S}}{\mu + d_{su} + k_{su}}, \\ \hat{I_{st}} = \dfrac{f \hat{\lambda_{0s}} \hat{S}}{k_{st} + \mu}, \\ \hat{I}_r = 0, \\ \hat{R} = \dfrac{k_{su} \hat{I_{su}} + k_{st} \hat{I_{st}}}{\mu + \omega}. \end{cases} \tag{4.2.9}$$

4. If $R_{0rC} > 1$ and $R_{0sC} > 1$, then either

i. $\hat{\lambda_r} = \hat{\lambda_s} = 0$, giving the DFE or

ii. $\hat{\lambda_s} = 0$ and $\hat{\lambda_r} \neq 0$, giving the resistant strain endemic equilibrium, $\hat{E}_r$ or

iii. $\hat{\lambda_s} \neq 0$ and $\hat{\lambda_r} = 0$, giving the sensitive strain endemic equilibrium, $\hat{E}_s$

or

iv. $\hat{\lambda_s} \neq 0$ and $\hat{\lambda_r} \neq 0$; in this case we have the following system

$$\begin{cases} \gamma_r \hat{\lambda}_r + \gamma_s \hat{\lambda}_s + (1 - R_{0rC}) = 0 \\ \gamma_r \hat{\lambda}_r + \gamma_s \hat{\lambda}_s + (1 - R_{0sC}) = 0. \end{cases} \tag{4.2.10}$$

This implies that $R_{0sC} = R_{0rC} = R_{0C}$. In this case we have two cases:

a. If $R_{0sC} \neq R_{0rC}$, then there is no endemic equilibria.

b. If $R_{0sC} = R_{0rC}$, then

$$\hat{\lambda_r} = \frac{R_{0C} - 1 - \gamma_s}{\gamma_r}.$$

In this case system (4.2.1) has a family of endemic equilibria given by

$$\begin{cases} \hat{V} = \dfrac{\nu \hat{S}}{\sigma + \mu}, \\ \hat{I_{su}} = \dfrac{(1-f)\hat{\lambda_s} \hat{S}}{\mu + d_{su} + k_{su}} \\ \hat{I_{st}} = \dfrac{f \hat{\lambda_s} \hat{S}}{k_{st} + \mu} \\ \hat{I_r} = \dfrac{(R_{0C} - 1 - \gamma_s)\hat{S}}{\gamma_r(\mu + d_r + k_r)} \\ \hat{R} = \dfrac{k_{su}\hat{I_{su}} + k_{st}\hat{I_{st}} + k_r \hat{I_r}}{\mu + \omega}. \end{cases} \tag{4.2.11}$$

4.3 Bifurcation diagrams and their interpretation

The threshold conditions determined by R_{0sC} and R_{0rC} can be rewritten using f and ν, which will make it more easy to understand the impact of varying

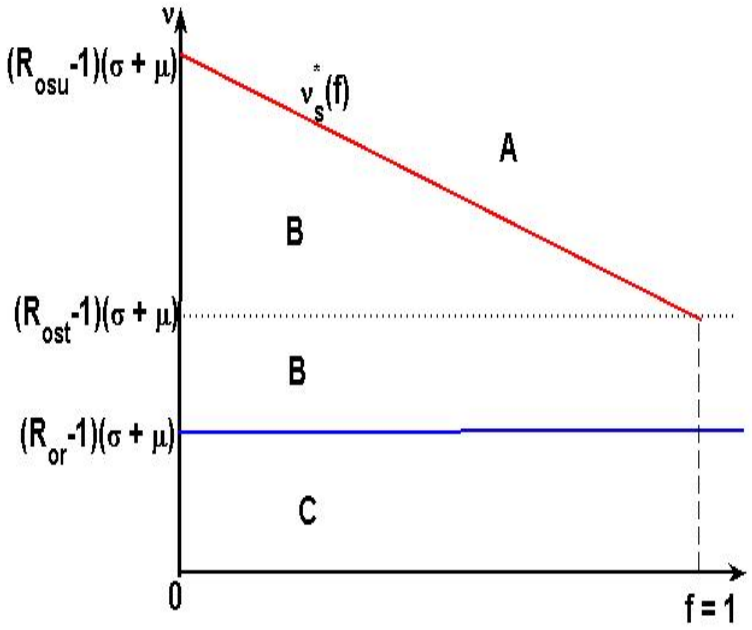


Figure 4.2: Bifurcation diagram in the (f, ν), plane for the cases $R_{0C} < 1$, (Region A), $R_{0sC} > 1$ and $R_{0rC} < 1$, (Region B) and $R_{0sC} > 1$ and $R_{0rC} > 1$ (Region C).

the treatment and vaccination rates. $R_{0sC} < 1$ if and only if

$$\nu > (\sigma + \mu)\left[R_{0su} - 1 - f(R_{0su} - R_{0st})\right] := \nu_s^*(f) \tag{4.3.1}$$

and $R_{0rC} < 1$ if and only if

$$\nu > (\sigma + \mu)(R_{0r} - 1) := \nu_r^*. \tag{4.3.2}$$

The proportion ν_r^* increases linearly with σ and R_{0r}. This means that when σ is high (waning effect is high) we need to vaccinate more people. The same applies to R_{0r}. In fact, when R_{0r} is high, more people are expected to be infected with the resistant strain. In this case it is necessary to vaccinate higher proportion of susceptible individuals to prevent them from being infected with

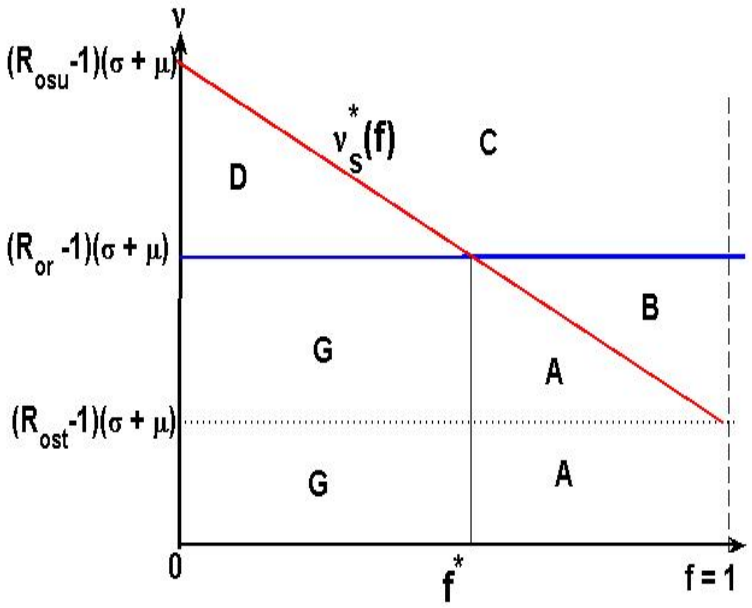


Figure 4.3: Bifurcation diagram in the (f, ν) plane for the cases $R_{0C} > 1$ and $\nu < \nu_r^*$ and $\nu < \nu_s^*(f)$ (Region A and G), $R_{0sC} < 1$ and $R_{0rC} > 1$ and $\nu < \nu_r^*$ and $\nu > \nu_s^*(f)$ (Region B) and $R_{0sC} > 1$ and $R_{0rC} > 1$ and $\nu > \nu_r^*$ and $\nu > \nu_s^*(f)$ (Region C) and $R_{0sC} > 1$ and $R_{0rC} < 1$ (Region D).

the resistant strain.

Moreover, $\nu_s^*(f)$ is the minimal value to be vaccinated when individuals are exposed to the sensitive strain only. This value decreases linearly with the rate at which people are treated, f, as well as $R_{0su} - R_{0st}$ which is the the reduction in the basic reproductive number of the sensitive strain that is due to treatment.

To carry out a bifurcation analysis of (4.1.1) we assume that treatment reduces the basic reproductive number of the sensitive strain, that is $R_{0st} < R_{0su}$. We distinguish the following cases:

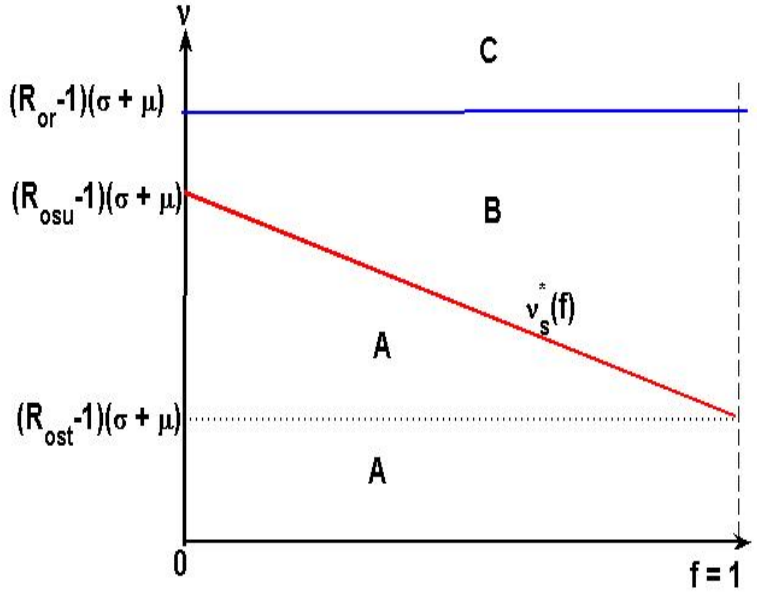


Figure 4.4: Bifurcation diagram in the (f, ν) plane for the cases $R_{0C} > 1$ and $\nu < \nu_r^*$ and $\nu < \nu^*(f)$ (Region A), $R_{0sC} < 1$ and $R_{0rC} > 1$ and $\nu < \nu_r^*$ and $\nu > \nu^*(f)$ (Region B) and $R_{0sC} < 1$ and $R_{0rC} < 1$ and $\nu > \nu_r^*$ and $\nu > \nu^*(f)$ (Region C).

1. $R_{0r} < R_{0st}$: represented in Figure 4.2.

2. $R_{0st} < R_{0r} < R_{0su}$: represented in Figure 4.3.

3. $R_{0su} < R_{0r}$: represented in Figure 4.4.

From bifurcation diagram (4.2) we observe that in region A, $\nu > \nu_s^*(f)$ and $\nu > \nu_r^*$, implying that $R_{0sC} < 1$ and $R_{0rC} < 1$. Therefore, the DFE is stable implying that there is no influenza infection at all. In region B, $\hat{E}_r$ exists and it is stable. In region C, both sensitive and resistant strains exist, since $R_{0r} < R_{0s}$, the sensitive strain (the one with the higher reproduction number) is stable.

From bifurcation diagram (4.4) we observe that in region A, both strains exist with the resistant strain (the one with the higher reproduction number) being stable. In region B, $\hat{E}_r$ is locally asymptotically stable. Finally in region C, the DFE is stable.

From bifurcation diagram (4.3) we observe that in region C, the DFE is stable. In region B, the resistant strain, $\hat{E}_r$ exists and it is locally asymptotically stable. In region D, the sensitive strain, $\hat{E}_s$ exists and it is locally asymptotically stable. In region A and G, both resistant and sensitive strains exist, but only the one with the higher basic reproductive number will be stable.
Notice that the two lines $\nu_s^*(f)$ and ν_r^*, intersect at $f^* = \dfrac{R_{0su} - R_{0r}}{R_{0su} - R_{0st}}$ and that when $f > f^*$ (resp. $f < f^*$) we have $R_{0r} < R_{0s}$ (resp. $R_{0r} > R_{0s}$). Therefore, in region A ($f > f^*$), $\hat{E}_r$ is the one that is stable while in region G, the equilibrium point $\hat{E}_s$ is stable.

4.4 Numerical simulations and discussions

In this section we present some numerical results which extend the mathematical analysis results and illustrate the impact of two important factors on controlling the disease. That is the rate at which susceptible individuals are vaccinated and the fraction of new sensitive strain cases being treated. We also confirm the stability of the equilibrium points numerically. We consider the following initial condition $S(0) = 8000, V(0) = 2000, I_{su}(0) = 200, I_{st} = 0, R(0) = 0$ for model (4.1.1).

According to CDC 2008 [2], the immunity obtained from vaccination lasts

Table 4.2: Parameter values used in the simulations for system 4.1.1.

Parameter	Parameter values
ν	$0.001 - 0.50$
σ	0.003
ω	0.003
δ	0.4
f	$0.0 - 0.9$
k_{su}	0.1667
k_{st}	0.1667

about one year, assuming that the average length of immunity induced by vaccine and by infection are the same, we choose $\sigma = \omega = 0.003(days^{-1})$. We consider different values of vaccination rate and treatment.

Note that for all the numerical simulations we consider the parameter values in Table (4.2) and only check the impact of antiviral treatment and vaccination by considering different values of f, ν.

When $R_{0C} < 1$, the population dynamics of infected individuals are represented in Figure (4.5). We observe that individuals infected with the sensitive strain (treated and untreated) and individuals infected with the resistant strain vanish, implying that the influenza virus dies out as time goes on. This is also shown in the bifurcation diagrams 4.2 and 4.4 in region A and C respectively. Therefore DFE is locally asymptotically stable when $R_{0C} < 1$.

When $R_{0sC} > 1$ and $R_{0rC} < 1$, the population dynamics of infected individuals are represented in Figure (4.6). We observe that individuals infected with the sensitive strain increase and reach their equilibrium point while the individuals infected with the resistant strain decrease and reach its equilibrium point. This is shown in the bifurcation diagram in figure 4.2 in region B. In this case, the equilibrium point for sensitive strain is locally asymptotically stable.

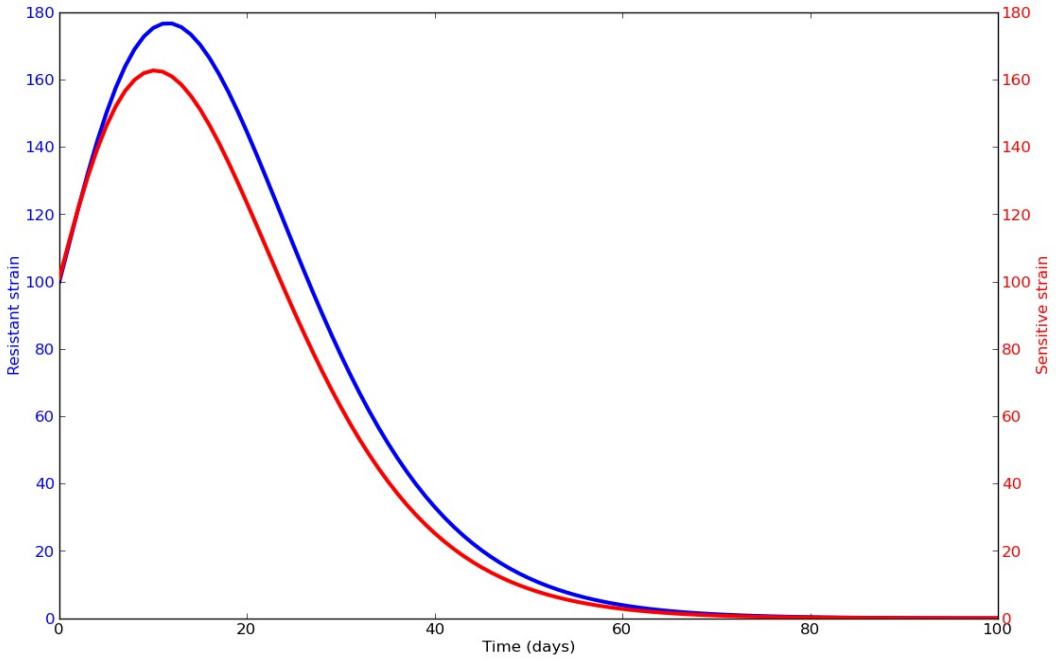


Figure 4.5: Population dynamics of system (4.1.1) when $R_{0C} < 1$ with the parameter values in Table 4.2 except that $\beta_r = \beta_s = 0.02835$.

When $R_{0sC} < 1$ and $R_{0rC} > 1$, the population dynamics of infected individuals are represented in Figure (4.7). We observe that the number of individuals infected with the resistant strain increase and reach their equilibrium point while the number of individuals infected with the sensitive strain decrease and reach its equilibrium point. In this case the equilibrium point for resistant strain is locally asymptotically stable. This is shown in the bifurcation diagrams 4.3 and 4.4 both in region B.

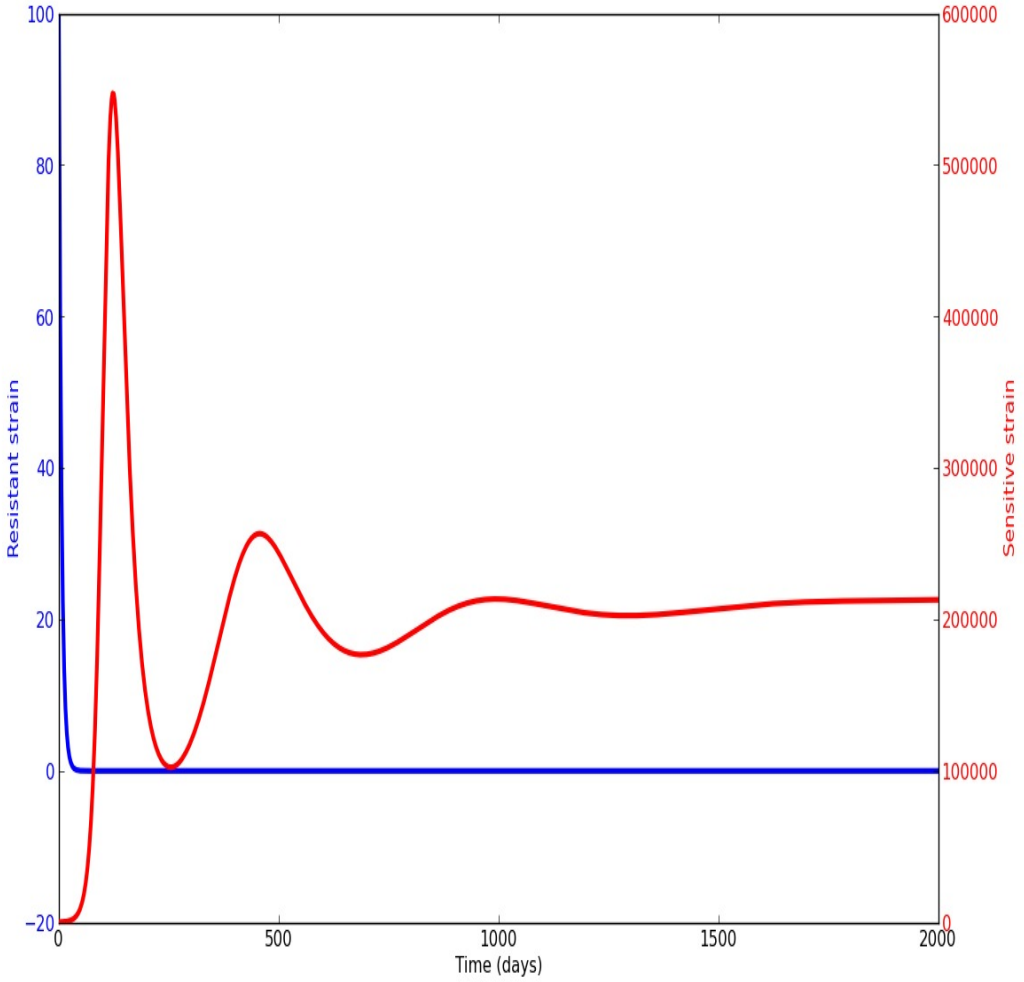


Figure 4.6: Population dynamics of system (4.1.1) when $R_{0sC} > 1$ and $R_{0rC} < 1$, with the parameter values in Table 4.2 except that $\beta_r = 0.0002835$ and $\beta_s = 0.2835$.

When $R_{0sC} > 1$ and $R_{0rC} > 1$, the transmission dynamics of infected individuals are represented in Figures (4.8). We observe that when the transmission

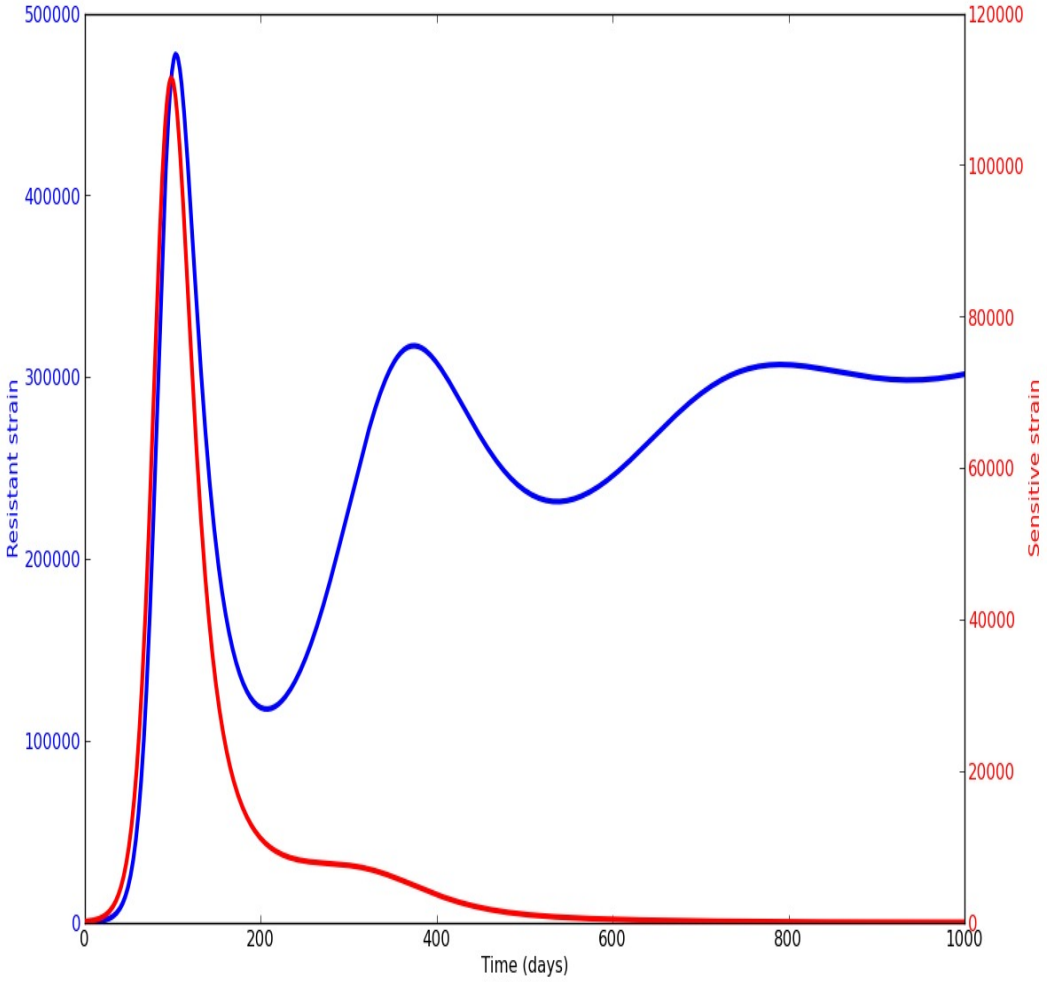


Figure 4.7: Population dynamics of system (4.1.1) when $R_{0sC} < 1$ and $R_{0rC} > 1$, with the parameter values in Table 4.2 except that $\beta_r = 3.009$ and $\beta_s = 0.2835$.

rates are equal and the treatment is not implemented both strains will persist. This means that the two endemic equilibria for both strains are locally

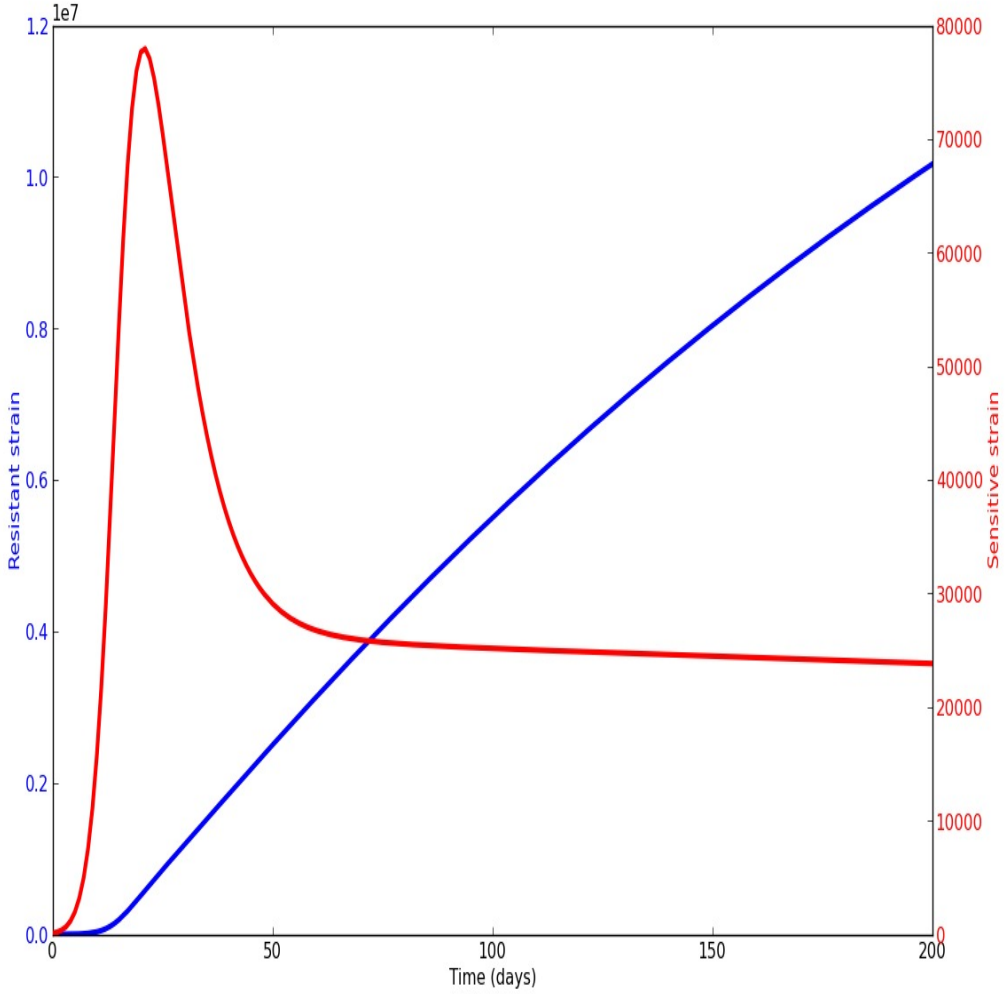


Figure 4.8: Population dynamics of system (4.1.1) when $R_{0sC} > 1$ and $R_{0rC} > 1$, with the parameter values in Table 4.2 except that $f = 0$, $\beta_r = 0.02835$ and $\beta_s = 0.2835$.

asymptotically stable as shown in Figure 4.3 region C.

In Figure (4.9) the population dynamics for both sensitive and resistant strain when $R_{0sC} < 1$ and $R_{0rC} > 1$, considering different values of f. We observe that when 50% of the susceptible individuals is treated, then the number of individuals infected with the sensitive strain will decrease while the number of individuals infected with the resistant strain increases and reaches its equilibrium point. This means that the resistant strain equilibrium point is locally asymptotically stability.

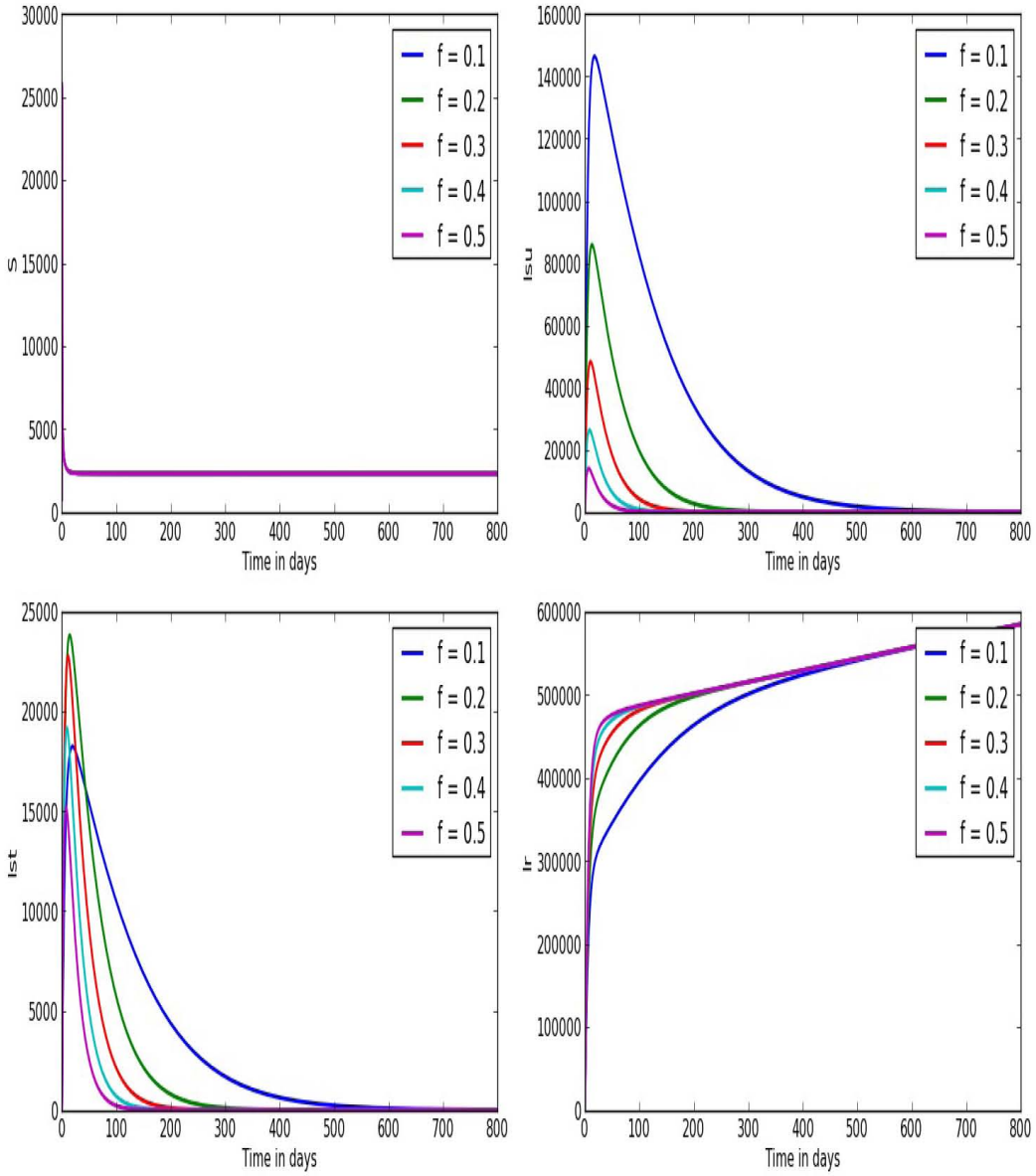


Figure 4.9: Population dynamics of system (4.1.1) considering different values of f.

Chapter 5

Discussion and concluding remarks

In this study we considered two compartmental models for influenza with sensitive and resistant strains. The first model considered a population which is divided into four disjoint classes: susceptible individuals, individuals infected with the sensitive strain, individuals infected with the resistant strain and recovered individuals. The second model considered a population which is divided into six disjoint classes: In addition to the ones for the first model we considered the class of individuals infected with the sensitive strain which is divided into two classes: untreated individuals and treated ones and vaccinated individuals.

We reviewed several recent studies on the influence of different influenza prevention and control measures including vaccination and antiviral treatment. In this study we considered the use of antiviral treatment and vaccination as the control measures in order to gain more insights on the implementation of control measures of influenza among human population.

In Chapter 3 we have developed and analysed a compartmental model that describes the transmission dynamics of influenza where control measures such as quarantine, vaccination and treatment are not implemented. We considered the resistant and sensitive strains, and a constant recruitment into each class. This model is the modification of the model in the "Modelling and analysis of influenza A (H1N1) on networks" [13] whereby only the transmission dynamics of influenza between susceptible, exposed, asymptotic, infected and recovered individuals were considered, but without considering the sensitive and resistant strains or emergency strain that may cause death.

The numerical analysis showed that when the basic reproduction numbers of both strains are less than one the two strains will die out. When at least one of the basic reproduction numbers is greater than one, the strain with the higher basic reproduction number is the one that will persists. In general, the sensitive strain is the one that is more dominant, but it can be eliminated by treatment. It has been shown mathematically that the DFE will be locally asymptotically stable when both basic reproduction numbers of both strains are less than one. Also, when at least one of the basic reproduction numbers is greater than one, the strain with the higher basic reproduction number is that one that will be locally asymptotically stable. These has also been confirmed using bifurcation theory.

In Chapter 4 we extended the model in Chapter 3 in order to incorporate antiviral treatment and vaccination. The numerical analysis showed that the more susceptible individuals get treated the more the number of individuals infected with the resistant strain increases, these imply that higher levels of treatment may lead to an increase of epidemic, and the extend to which this

occurs depends on the other factors like the rates of resistance development and vaccination. This suggests that vaccination and antiviral treatment should be implemented appropriately. The resistant strain might be due to the new strain or unknown strain or emergence strain during the cause of the outbreak, and obviously when the new strain emerges we can not get the appropriate treatment as soon as possible. So it is important for us to gain more insights on how we can prepare for any new strain. These can be controlled by vaccinating as many people as possible before the outbreak starts. We also applied bifurcation theory to show the stability of endemic equilibria using the reproduction numbers and taking into consideration the effect of treatment and vaccination. The bifurcation results corresponds with what we have observed in the numerical simulations.

The model with vaccination and treatment can be extended in order to incorporate some more control measures such as quarantine, isolations, media coverage and new strain.

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